



**World Health
Organization**

**Department of Immunization,
Vaccines and Biologicals (IVB)**

SAGE

October 2016

**Strategic Advisory Group of Experts
on Immunization
18 - 20 October 2016**

**Centre International de Conférences (CICG)
Geneva, Switzerland**



SAGE October 2016

This booklet contains key background documents for the
meeting of the
Strategic Advisory Group of Experts (SAGE) on immunization
18 - 20 October 2016

Further documents can be found online at the SAGE
work space web site:

<http://www.who.int/immunization/sage/meetings/2016/october/en/>

Table of Contents – October 2016 SAGE meeting

Agenda	1
List of SAGE members	9
SAGE Terms of References	11
Current SAGE Working Groups	17
Provisional list of participants	24
Session 1: Report from IVB Director	
1. Meeting of the Strategic Advisory Group of Experts on immunization, April 2016 – conclusions and Recommendations. WER 2016;91:266-84	40
2. SAGE tracking record of recommendations and action points	59
3. Report of the AFRO Regional Immunization Technical Advisory Group Meeting, 5-8 July 2016, Brazzaville, Congo	82
4. Ministerial conference on immunization in Africa	112
5. Ad-hoc Virtual TAG Meeting 2016- XXIV Meeting of the Technical Advisory Group on Vaccine-preventable Diseases, 13 May 2016, Washington, DC, USA	116
6. Seventh Meeting of the South-East Asia Regional Immunization Technical Advisory Group (SEAR-ITAG): Conclusions and recommendations, New Delhi, India, 06–10 June 2016	136
7. 25th Meeting of the Technical Advisory Group on Immunization and Vaccine Preventable Diseases, 26-29 July 2016, Manila, Philippines. Conclusions and recommendations	156
Session 2: Report from Gavi, the Vaccine Alliance	
1. Update on the 22-23 June 2016 Gavi Board Meeting.	172
Session 3: Report from other Advisory Committees on Immunization	
1. Global Advisory Committee on Vaccine Safety (GACVS), 15-16 June 2016. WER 2016;91:341-8	174
2. Summary of GACVS reviews of HPV vaccines	182
3. Report from the World Health Organization's Third Product Development for Vaccines Advisory Committee (PDVAC) meeting, Geneva, 8-10th June 2016	196
4. Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC) summary of conclusions and recommendations, 30 May-1 June 2016 meeting. WER 2016;91:389-96	216
Session 4: Report activities from international immunization partners (No background documents provided)	
Session 5: Polio eradication initiative	
1. SAGE Polio WG - notes from August 2016 meeting	224
2. Fractional-dose inactivated poliovirus vaccination campaign, Telangana state, India, June 2016. WER 2016; 91:397–404	232
3. Update on Vaccine-Derived Polioviruses — Worldwide, January 2015–May 2016. MMWR August 5, 2016 / 65(30);763–9	239
4. Cessation of Use of Trivalent Oral Polio Vaccine and Introduction of Inactivated Poliovirus Vaccine Worldwide, 2016. MMWR (to be published) or WER version WER 2016;91:421-7	246
Session 6: Measles and rubella elimination	
1. Measles and Rubella Global Strategic Plan 2012-2020 Midterm Review	253
2. WHO Policy Recommendation on Measles Second Dose (MCV2): Considerations for removing the criteria for introduction	303

Session 7: Maternal and neonatal tetanus elimination and overall tetanus prevention	
1. Report of the SAGE Working Group on Maternal and Neonatal Tetanus Elimination and Broader Tetanus Prevention	313
2. Tetanus vaccine WHO position paper. WER 2006;20: 198-208	340
Session 8: Global Vaccine Action Plan (GVAP) Progress report	
1. Draft 2016 Mid Term Review of the Global Vaccine Action Plan	351
Session 9: Hepatitis B vaccination	
1. Background summary, conclusions and recommendations on Hepatitis B containing vaccines	373
Session 10: Human Papillomavirus (HPV) vaccines	
1. Background paper: Schedules and strategies for human papillomavirus (HPV) immunization	415
2. See Summary of GACVS reviews of HPV vaccines in Session 3	182
Session 11: Yellow Fever	
1. Executive summary	441
2. Global strategy to eliminate yellow fever epidemics (EYE)	443
3. Fractional dose yellow fever vaccine as a dose-sparing option for outbreak response. WHO secretariat information paper, 20 July 2016	498
4. Yellow fever mass vaccination campaign using fractional dose in Kinshasa	521
5. Short-term research priorities for dose-sparing of YF vaccine (Revised version 26 September 2016)	526



Agenda

Meeting of the Strategic Advisory Group of Experts on Immunization (SAGE)
18 - 20 October 2016
Centre International de Conférences Genève (CICG), Geneva

Tuesday, 18 October 2016

Time	Session	Purpose of session, target outcomes and questions for SAGE	Duration
8:30	Welcome – introduction of participants J. Abramson, Chair of SAGE.		20 min.
8:50	Report from Director, IVB - Session 1 Global report including key updates and challenges from regions. J.-M. Okwo-Bele, WHO. 40 min. Discussion: 1h 20 min.	FOR INFORMATION	2h
09:50	Coffee/Tea break	Break	30 min.
10:20	Report from Director, IVB – Session 1, contd. Discussion contd.		
11:20	Report from Gavi, the Vaccine Alliance - Session 2 Report from Gavi, the Vaccine Alliance. A. Nguyen, Gavi, the Vaccine Alliance. 20 min. Discussion: 20 min.	FOR INFORMATION	40 min.
12:00	Lunch	Break	1h 30 min.

13:30	<p>Reports from other Advisory Committees on Immunization – Session 3</p> <p>Report of the Global Advisory Committee on Vaccine Safety (GACVS). R. Pless, Chair of GACVS. 10 min.</p> <p>Discussion: 10 min.</p> <p>Product Development for Vaccines Advisory Committee (PDVAC) D. Kaslow, Chair of PDVAC. 10 min.</p> <p>Discussion: 10 min.</p> <p>Report of the Immunization and vaccines related implementation research advisory committee (IVIR-AC), R. Breiman, Chair of IVIR-AC. 10 min.</p> <p>Discussion: 10 min.</p>	FOR INFORMATION	1h
14:30	<p>Report of activities from international immunization partners - Session 4</p> <p>Bill and Melinda Gates Foundation (BMGF), O. Levin, BMGF. 20 min.</p> <p>Discussion: 20 min.</p> <p>World Bank, TBD, World Bank 20 min.</p> <p>Discussion: 20 min.</p>	<p>FOR INFORMATION</p> <p>Continuation of the series of presentations initiated in October 2015 to be held at SAGE meetings on the immunization-related activities of partners working in the field of immunization.</p>	1h 20 min.
15:50	Coffee/tea break	Break	30 min.
16:20	<p>Polio eradication initiative - Session 5</p> <p>Objective of the session and overview of Global Polio Eradication Initiative, M. Zaffran, WHO. 20 min.</p> <ul style="list-style-type: none"> ▪ WPV and cVDPV2 elimination ▪ Other objectives in the GPEI Strategy Plan (2013-18) <p>Updates on implementation of OPV2 withdrawal, D. Chang-Blanc, WHO. 20 min</p> <p>Discussion: 20 min</p>	<p>FOR INFORMATION AND DISCUSSION</p> <p>This session will include an update on the switch and the progress with polio eradication and an initial discussion on post eradication.</p> <p>To inform and update SAGE on the:</p> <ul style="list-style-type: none"> • Current status of the polio eradication program 	2h 30 min.

	<p>Report from SAGE Polio WG, Y. AL-Mazrou, Chair of the Polio WG. 20 min.</p> <ul style="list-style-type: none">▪ Summary of WG meeting▪ Future immunization policy: Updates <p>Discussion: 1h 10 min.</p>	<ul style="list-style-type: none">• Update on implementation of OPV2 withdrawal and remaining issues• Discussions on future immunization policy after OPV withdrawal and update on the implementation of biocontainment of polioviruses <p>To ask for SAGE's guidance on:</p> <ul style="list-style-type: none">• Options for post-OPV immunization policy for further considerations	
18:50	End of Day		
19:00	Cocktail		

Wednesday, 19 October 2016

8:00	Measles and rubella elimination - Session 6 Global measles and rubella update, P. Strebel, WHO. 20 min. Findings and recommendations of the Mid Term Review of the measles and rubella strategic plan 2012-2020, W. Orenstein, Emory University. 30 min. Discussion: 60 min. Measles second dose introduction criteria, N. Turner, SAGE member, 15 min. Discussion: 25 min.	FOR DISCUSSION AND DECISION FOR DISCUSSION <ul style="list-style-type: none"> To review the current status of global measles and rubella control and regional elimination. FOR DECISION <ul style="list-style-type: none"> SAGE is requested to review the Mid Term Review findings and recommendations and endorse the recommendations. SAGE is requested to decide on whether or not to remove the introduction criteria for MCV2. 	2h 30min.
10:30	Coffee/tea break	Break	30 min.
11:00	Maternal and neonatal tetanus elimination and overall tetanus prevention - Session 7 Introduction, K. Johansen, Chair of Working group on maternal and neonatal tetanus elimination and overall tetanus prevention, 5 min. Update on the current MNTE strategy, achievements, successes and challenges including country experiences, A. Raza, UNICEF, 15 min. Discussion: 10 min. Broader tetanus prevention: Impact of current tetanus immunization programmes and need for acquiring broader tetanus prevention, R. Steinglass, Members of the Working group on maternal and neonatal tetanus elimination and overall tetanus prevention, 15 min. Discussion: 10 min.	FOR DECISION Based on its working group input, SAGE will be expected to provide recommendations on: 1. resetting the agenda, with interim milestones, for achieving MNTE; 2. steps that could be taken to increase visibility and political advocacy of MNTE; 3. how to overcome known and anticipated bottlenecks to achieving MNTE, including recommendations on how achieving the above outcomes will require different approaches by setting or typology; 4. strategies for sustaining MNTE elimination in countries that have achieved MNTE with targeted immunization strategies, including recommendations on methods for documenting sustained elimination;	2h 30 min

	Review of key conclusions and recommendations by the working group, K. Johansen, Chair of Working group on maternal and neonatal tetanus elimination and overall tetanus prevention, 35 min. Discussion: 1h	5. strategies to achieve broader tetanus prevention (i.e. including all age groups and both genders; 6. any necessary adjustments to the policy recommendations in the WHO tetanus position paper.	
13:30	Lunch	Break	1h
14:30	Global Vaccine Action Plan (GVAP): Progress report - Session 8 The GVAP Secretariat Report 2016: Update on process, new indicators, actions taken by the secretariat in response to previous reports, T. Cherian (on behalf of the Secretariat of the Decade of Vaccines Working Group), WHO. 15 min. Discussion: 15 min. Summary of GVAP implementation progress review and recommendations for corrective actions at the mid-term of the Decade of Vaccines, A. Cravioto, Member of the SAGE Decade of Vaccines Working Group. 30 min. Discussion: 2h	FOR DISCUSSION AND DECISION SAGE will be expected to produce an independent annual report on progress with the Decade of Vaccines Global Vaccine Action Plan. Specially, SAGE will be asked to: <ul style="list-style-type: none"> Review the DoV WG "Assessment report on DoV progress 2016" based on the "GVAP Secretariat report 2016", regional reports on the implementation of regional vaccine action plans, priority country reports and some Independent stakeholder submissions. Make recommendations on any necessary changes to the formulation of the indicators, operational definitions and/or the processes for data collection. Identify successes, challenges and areas where additional efforts or corrective actions by countries, regions, partners, donor agencies or other parties, are needed. Provide recommendations and corrective actions for Members States, regions, partners, donor agencies "SAGE Assessment report on the Decade of Vaccines progress" which will be the basis of the "progress report" for the WHO Executive Board and World Health Assembly.	
16:00	Coffee/tea break	Break	30 min.
16:30	Global Vaccine Action Plan (GVAP): Progress report - Session 8, Contd.		
18:00	End of day		

Thursday, 20 October 2016

08:00	<p>Hepatitis B vaccination - Session 9</p> <p>Introduction and key questions for the session. K. Johansen, SAGE member. 5 min.</p> <p>Hepatitis B infection -related disease burden, Immunogenicity and safety of hepatitis B vaccine schedules and thermostability of hepatitis B vaccines. F. de la Hoz Restrepo, Colombia National University. 25 min.</p> <p>Observed and forecasted impact of different hepatitis B immunization schedules and strategies. J. Edmunds, London School of Hygiene and Tropical Medicine. 20 min.</p> <p>Conclusions and proposed recommendations for SAGE. K. Johansen, SAGE member. 10 min.</p> <p>Discussion: 1 hr.</p>	<p>FOR DECISION</p> <p>Present SAGE with updated evidence on hepatitis B infection-related burden, immunogenicity and safety of hepatitis B containing vaccines, the impact of hepatitis B containing vaccines immunization programmes and the thermostability of the monovalent formulation. Focus is on evidence relevant to low- and middle-income countries.</p> <p>Request SAGE's consideration of the following questions:</p> <ul style="list-style-type: none"> • Do the current schedule recommendations require any modifications? • What is the impact of the vaccination programme on the epidemiology of hepatitis B when providing a timely vaccine birth dose? • Does the available evidence support flexibility in the requirement for cold chain storage of hepatitis B vaccines in order to expand the delivery of the birth dose? <p>SAGE recommendations may be used to update the 2009 WHO position paper on the use of hepatitis B vaccines.</p>	2h
10:00	Coffee/tea break	Break	30 min.
10:30	<p>HPV vaccines - Session 10</p> <p>Introduction and key questions for the session. A. Pollard, SAGE Member. 5 min.</p> <p>Update on HPV vaccine introduction and programmatic perspective. I. Ogbuanu, WHO. 15 min.</p>	<p>FOR DECISION</p> <p>Present SAGE with updated evidence on HPV-related burden, HPV vaccines, impact of HPV immunization programmes, and modelling of impact of HPV immunization schedules and strategies. Focus is on evidence relevant to low- and middle-income countries.</p> <p>Request SAGE's consideration of the following questions:</p>	2h15min

	<p>HPV-related disease burden and effects of different HPV immunization schedules and strategies. M. Ramsay, Public Health England. 20 min.</p> <p>Observed and forecast impact of different HPV immunization schedules and strategies. M. Brisson, Laval University. 20 min.</p> <p>Conclusions and proposed recommendations for SAGE. A. Pollard, SAGE Member. 15 min.</p> <p>Discussion: 1 h</p>	<ul style="list-style-type: none"> What is the incremental effectiveness and cost-effectiveness for cervical cancer prevention of different HPV vaccines based on girls-only immunization? What is the incremental effectiveness and cost-effectiveness for prevention of HPV-related diseases of adolescent gender-neutral HPV immunization compared to girls-only HPV immunization? What is the incremental effectiveness and cost-effectiveness for cervical cancer prevention of multiple age cohort HPV immunization of females (within a defined age range) compared to single age cohort immunization of girls-only or of both girls and boys aged 9–13 years? <p>SAGE recommendations may be used to update WHO position paper on HPV vaccines, which was published in October 2014.</p>	
12:45	Lunch	Break	1 h
13:45	<p>Yellow Fever - Session 11</p> <p>Introduction. C. Siegrist, SAGE member. 5 min.</p> <p><i>Part 1: Long term Yellow Fever strategy</i></p> <p>Epidemiology and risk of yellow fever in current context. O. Tomori, Redeemers University, 15 min.</p> <p>Yellow fever vaccine supply: Projected availability and opportunities for scaling up. A. Costa, WHO, 10 min.</p> <p>Global Strategy for Eliminating Yellow fever Epidemics (EYE). O. Ronveaux, WHO, 15 min.</p> <p>Discussion: 1 hr.</p> <p><i>Part 2: Options for emergency surge capacity</i></p>	<p>FOR DISCUSSION AND DECISION</p> <p>SAGE is asked to provide feedback on the general approach of the "Global Strategy for Eliminating Yellow fever Epidemics (EYE)".</p> <p>SAGE is asked to provide recommendations and research priorities for fractional dose use of Yellow fever vaccine as a response to major outbreaks.</p>	3h

	<p>Introduction and context to surge capacity needs. J. Hombach, WHO, 5 min.</p> <p>Fractional dosing of Yellow fever vaccines: review of vaccine potency & stability information, available evidence, and evidence gaps. A. Barrett, University of Texas Medical Branch. 15 min.</p> <p>Feedback from the DRC Yellow fever fractional dose campaign, R. Mihigo, WHO-AFRO, 10 min.</p> <p>Secretariat recommendations and key research needs. J. Hombach, WHO. 5 min.</p> <p>Discussion 40 min.</p>		
16:45	Closing		20 min.
17:00	End of meeting		

**Meeting of the WHO Strategic Advisory Group of Experts (SAGE) on Immunization
12-14 April 2016
Geneva, Switzerland**

SAGE members

<p>Professor Jon S. Abramson (Chair) Professor Department of Pediatrics Wake Forest University Baptist Medical Centre Medical Center Blvd 27104 Winston-Salem United States of America</p>
<p>Dr Yagob Yousef Al-Mazrou Secretary General Council of Health Services Riyadh 12628 Saudi Arabia</p>
<p>Dr Alejandro Cravioto Independent Consultant 48339 Puerto Vallarta Mexico</p>
<p>Dr Ilesh Jani Director General Instituto Nacional de Saúde (INS) Ministry of Health PO Box 264 Maputo Mozambique</p>
<p>Dr Jaleela Jawad Head, Immunization Group and EPI Manager Public Health Directorate Ministry of Health Manama Bahrain</p>
<p>Dr Kari Johansen Expert Influenza and other Vaccine Preventable Diseases Surveillance and Response Support Unit European Centre for Disease Prevention and Control Tomtebodavägen 11A 171 83 Stockholm Sweden</p>
<p>Professor Terence Nolan Head, Department of Public Health Melbourne School of Population Health The University of Melbourne Level 5 207 Bouverie Street Carlton Victoria 3010 Australia</p>
<p>Dr Katherine L. O'Brien Professor Department of International Health John Hopkins Bloomberg School of Public Health Baltimore 21231 MD United States of America</p>

<p>Professor Andrew Pollard Professor of Paediatric Infection and Immunity Depart of paediatrics University of Oxford Room 02-46-07 Level 2, Children's Hospital Oxford OX3 9DU United Kingdom</p>
<p>Dr Firdausi Qadri Senior Director Infectious Diseases Division International Centre for Diarrhoeal Diseases Research, Bangladesh 1212 Dhaka Bangladesh</p>
<p>Professor Claire-Anne Siegrist Head, WHO Collaborating Centre for Neonatal Vaccinology Department of Pediatrics & Pathology-Immunology Centre Médical Universitaire 1 rue Michel Servet 1211 Genève 4 Switzerland</p>
<p>Dr Piyani Tharmaphornpilas Senior Medical Adviser, Disease Control Ministry of Public Health Tiwanon Road Taladkwan, Muang Nonthaburi 11000 Thailand</p>
<p>Dr Nikki Turner Associate Professor, Director Immunisation Advisory Centre Department of General Practice and Primary Health Care The University of Auckland 6012 Wellington New Zealand</p>
<p>Professor Fredrick Were Dean School of Medicine University of Nairobi P.O. Box 30588 00202 Nairobi Kenya</p>
<p>Dr Charles Shey Wiysonge Professor & Deputy Director Centre for Evidence-based Health Care Stellenbosch University 7460 Ruyterwacht South Africa</p>

Strategic Advisory Group of Experts (SAGE)

Terms of reference

Functions

SAGE is the principal advisory group to WHO for vaccines and immunization. It is charged with advising WHO on overall global vaccination policies and strategies, ranging from vaccines and technology, research and development, to delivery of vaccination and its linkages with other health interventions. SAGE's remit extends to the control of all vaccine-preventable diseases as part of an integrated, people centred platform of disease prevention that spans the human life-course and in the context of health systems strengthening.

SAGE advises the WHO Director-General specifically on the:

1. adequacy of progress towards the achievement of the goals of control of vaccine-preventable diseases worldwide such as those laid out in the Decade of Vaccines Global Vaccine Action Plan 2011-2020.
2. major issues and challenges to be addressed with respect to achieving the disease control goals, including issues and challenges to achieving and sustaining high and equitable vaccination coverage;
3. immunization programme response to current public health priorities;
4. major general policies, goals and targets including those related to vaccine research and development;
5. adequacy of WHO's strategic plan and priority activities consistent with its mandate and considering the comparative advantages and the respective roles of partner organizations;
6. engagement of WHO in partnerships that will enhance achievement of global immunization goals.

Membership

SAGE comprises 15 independent experts, who shall serve in their personal capacity and represent a broad range of affiliations and a broad range of disciplines encompassing many aspects of immunization and vaccines. Members should refrain from promoting the policies and views and products of the institution for which they work.

SAGE members are recruited and selected as acknowledged experts from around the world in the fields of epidemiology, public health, vaccinology, paediatrics, internal medicine, infectious diseases, immunology, drug regulation, programme management, immunization delivery, health-care administration, health economics, and vaccine safety.

The membership of SAGE shall seek to reflect a representation of:

1. professional affiliation (e.g., academia, medical profession, clinical practice, research institutes, and governmental bodies including national immunization programmes, public health departments and regulatory authorities);
2. major areas of expertise (e.g., vaccine research, vaccine and immunization safety, optimization of immunization schedules, vaccine delivery, disease control strategies, impact monitoring); and
3. the strategic focus areas of the WHO's vaccine and immunization work including vaccines norms and standards, vaccine regulation, vaccine programme management, delivery and surveillance and monitoring, and vaccine research & development.

SAGE members, including the Chairperson and the Vice-Chairperson, are appointed by the WHO Director-General. Members are selected upon the proposal of an independent selection panel including representatives of key partner organizations. A public call for nominations is issued. After determination of eligibility, nominations are submitted to the selection panel. Members will be selected on the basis of their qualifications and ability to contribute to the accomplishment of SAGE's objectives. Renewals of term are also submitted to the selection panel.

Consideration will be given to ensuring appropriate geographic representation and gender balance. Chairs of regional technical immunization advisory groups are not eligible to serve on SAGE but are invited to attend SAGE meetings. WHO staff and United Nations staff members are not eligible to serve on SAGE.

Members of SAGE shall be appointed to serve for an initial term of three years. This three-year term may only be renewed once. To allow for continuity and efficiency, the Chairperson of SAGE is expected to act as Chairperson for a minimum of three years, not taking into account if he/she has already served three years or has been renewed for a further three years as a member of SAGE. He/she needs however, to be a member of SAGE for a minimum of one year before taking up Chairpersonship.

Prior to being considered for SAGE membership, nominees shall be required to complete a WHO Declaration of Interests

All papers presented to SAGE, which may include pre-publication copies of research reports or documents of commercial significance, shall be treated as confidential. SAGE deliberations are confidential and may not be publicly disclosed by SAGE members. Therefore, prior to confirmation by WHO of their appointment as SAGE members, SAGE nominees shall be required to sign a Confidentiality Undertaking.

A register of members' interests and signed confidentiality agreements shall be maintained by WHO.

Version: 19 September 2016

Membership in SAGE may be terminated for any of the following reasons:

1. failure to attend two consecutive SAGE meetings;
2. change in affiliation resulting in a conflict of interest or involvement in activities resulting in a conflict of interest incompatible with serving on SAGE; and
3. a lack of professionalism involving, for example, a breach of confidentiality.

Meetings and operational procedures

SAGE meetings occur biannually, in April and October, and are scheduled 3 years ahead. The frequency of meetings may, however, be adjusted as necessary. The WHO Secretariat will work with SAGE members and key global stakeholders to develop SAGE priorities and workplans as well as specific meeting agendas.

SAGE members are asked to update their declared interests before each meeting. SAGE members with potentially conflicting interests will not participate in deliberations on the specific topic(s) for which they would have a conflict of interest. SAGE member's relevant interests will be made publically available four weeks in advance of the meeting for public comments. Background documents, presentations, final agenda and final list of participants are posted after the meeting are posted on the SAGE public website after the meeting.

Decisions or recommendations by SAGE will, as a rule, be taken by consensus.

The WHO Regional Offices, Chairs of regional technical immunization advisory groups and Chairs of relevant WHO technical advisory committees will be invited to participate in SAGE meetings and contribute to the discussions. The major global immunization stakeholders such as UNICEF, the Secretariat of Gavi, the Vaccine Alliance, and representatives of civil society organizations will also be invited to attend and contribute to SAGE meetings.

WHO may also invite other observers to SAGE meetings, including representatives from non-governmental organizations, international professional organizations, technical agencies, partner organizations, Chairs and members of national technical advisory groups on immunization as well as associations of manufacturers of vaccines and immunization technologies and representatives from the manufacturing companies.

Additional experts may be invited to meetings, as appropriate, to further contribute to specific agenda items. Observers and invited experts will not participate in the decision making process but will be allowed to contribute to the discussions as directed by the Chairperson.

SAGE reports to the WHO Director-General. The SAGE Chairperson will debrief the Director-General (or designee) following each SAGE meeting. The conclusions and recommendations of SAGE meetings shall be published in the Weekly Epidemiological Record and posted on the website within two months of each SAGE meeting. These conclusions and recommendations will be translated into all the WHO headquarters official languages. A brief summary report of the meeting shall also be posted on the SAGE website the day after the SAGE meeting.

Roles and responsibilities of SAGE members

Members of SAGE have a responsibility to provide WHO with high quality, well considered advice and recommendations on matters described in these SAGE terms of reference. Members play a critical role in ensuring the reputation of SAGE as an internationally recognized advisory group in the field of immunization. In keeping with SAGE's mandate to provide strategic advice rather than technical input, members will be committed to the development and improvement of public health policies.

SAGE has no executive or regulatory function. Its role is solely to provide advice and recommendations to the Director-General of WHO. This includes providing advice and recommendations on urgent public health issues as needed.

SAGE members may be approached by non-WHO sources for their views, comments and statements on particular matters of public health concern and asked to state the views of SAGE. SAGE members shall refer such enquiries to WHO.

SAGE members will not be remunerated for their participation in SAGE; however, reasonable expenses such as travel expenses incurred by attendance at SAGE or related meetings will be compensated by WHO.

SAGE members are expected to endeavour to attend all biannual meetings. Further active participation will be expected from all SAGE members throughout the year, including participation in SAGE Working Groups, video and telephone conferences as well as frequent interactions via e-mail. Review of documents may also be solicited. SAGE members may be requested to participate as observers in other important WHO or partners meetings. As a result SAGE members are expected to commit to invest a substantial amount of their time to SAGE.

The secretariat of SAGE is ensured by the Immunization Policy Unit of the Department of Immunization, Vaccines and Biologicals. The function of Executive Secretary is ensured by the Senior Health Advisor who directs this Unit.

SAGE will be kept informed by WHO and partner agencies on progress concerning implementation of strategies and the attainment of objectives at country and regional level. SAGE will also be informed of conclusions and recommendations from WHO relevant technical advisory groups including regional technical advisory groups.

SAGE Working Groups are established as resources intended to increase the effectiveness of SAGE deliberations by reviewing and providing evidence-based information and options for recommendations together with implications of the various options to be discussed by SAGE during one of its biannual meetings. These Working Groups are normally established on a time-limited basis to help address specific questions identified by SAGE when the issue is particularly complicated or time-consuming and could not be addressed by an existing standing WHO advisory committee. The need and charge for a Working Group is discussed and agreed during SAGE meetings. The purpose, structure and functioning of the Working Groups is described in detail in Annex 1 (Purpose, structure and functioning of the Strategic Advisory Group of Experts on Immunization (SAGE) Working Groups).

For its proceedings, SAGE shall follow an evidence-based review process as outlined in the SAGE guidance document on evidence-based vaccine-related recommendations

(http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf?ua=1).

More detailed information on SAGE operating procedures is available on the SAGE website

(http://www.who.int/immunization/sage/working_mechanisms/en/).

Purpose, structure and functioning of the Strategic Advisory Group of Experts on Immunization (SAGE) Working Groups

Purpose and decision to establish a SAGE Working Group

SAGE Working Groups are established as resources intended to increase the effectiveness of SAGE deliberations by reviewing and providing evidence-based information and options for recommendations together with implications of the various options to be discussed by SAGE in an open public forum.

These Working Groups are normally established on a time limited basis to help address specific questions identified by SAGE when the issue cannot be addressed by existing standing WHO advisory committees. Some Working Groups such as that on polio eradication or the Decade of Vaccines Working Group can be established for a number of years.

The need for and creation of a Working Group is discussed and agreed during SAGE meetings, preparatory teleconferences for SAGE meetings, or in case of urgency via email interaction.

Terms of reference of the Working Groups and identification of needed expertise to serve on the Working Group
Each Working Group operates under specific terms of reference (TORs). These TORs are defined within 30 days of the SAGE decision to establish the Working Group.

Proposed TORs and related expertise to serve on the Working Group are developed jointly by the SAGE member serving as Working Group Chair, the Lead WHO technical staff and SAGE Executive Secretary. Draft TORs and related expertise are reviewed by SAGE members. Final decision is taken jointly by the SAGE Chair, Working Group Chair, SAGE Executive Secretary, and the Director of the Department of Immunization, Vaccines and Biologicals.

Working Group composition and selection of membership

Each Working Group should include two or more SAGE members (one of whom functions as Chair), and additional subject matter experts serving in their own individual capacity and with a view to meet the identified needed expertise for the group. SAGE members and other experts who have identified conflicts of interest cannot serve on the Working Group charged with responsibility in the identified areas of conflict. WHO staff (one of whom functions as the Working Group technical lead serve as secretariat to the Working Group. In some instances other UN or non UN agencies can be co-opted as part of the secretariat. For the selection of experts to serve on a Working Group, a public call for nomination for Working Group members will be posted on the SAGE website together with the relevant TORs of the Working Group and indication of the desirable expertise. SAGE members, regional offices, diplomatic missions, WHO staff and key partner organizations will also be approached to propose potential nominations. Nominees will be requested to provide both a Curriculum Vitae and a completed Declaration of Interests form prior to being considered for membership on the Working Group.

The selection panel, comprised of the SAGE Chair (or Vice-Chair), the Working Group Chair, the SAGE Executive Secretary and lead WHO technical staff will select Working Group members from the pool of nominees. In addition to meeting the required expertise and avoidance of nominating individuals with conflicts of interest, attention will be given to ensure proper diversity including geographic and gender representation. In general, Chairs of regional technical immunization advisory groups are not eligible to serve on SAGE Working Groups. Should experts be appointed as Chair of a regional technical immunization advisory group after their nomination as member of a Working Group and for SAGE members while still serving on the group after they rotate out of SAGE, they may continue to serve on the Working Group.

For Working Groups which terms of reference require proceedings over a number of years, if a SAGE member rotates out of SAGE while the Working Group is still active, then he/she remains on the Working Group but a new SAGE member should be enrolled to serve on the group. A new SAGE member should be appointed as Working Group Chair when the previous Chair rotates out of SAGE. For Working Groups having proceedings spanning over a number of years, the same rotation process as applied to SAGE membership should be applied i.e. two 3-year terms. The renewal is being determined by a selection panel comprised of the SAGE Chair (or Vice-Chair), the Working Group Chair, lead WHO technical staff and the SAGE Executive Secretary and is based on the contribution of the member to the group. If members resign for personal reasons, are no longer eligible to serve on the group due to arising conflicts of interest, or are unable to meaningfully contribute to the proceedings of the group, they can be replaced with first considering an appointment from the list of initial candidates to join the group. The decision will be made as for the selection of candidates (see above). If no one from this list is suitable then another expert could be solicited and co-opted without resourcing to an open call for nomination.

The size of the Working Group should not exceed 10-12 members and will be adjusted based on the need for expertise and representation.

On rare occasions joint reviews of evidence by SAGE and another area WHO advisory committee (focusing on another area than immunization but with expertise and relevance to the topic being considered) may have to be organized. As a result a SAGE Working Group may be formed in conjunction with this other solicited advisory committee. In this instance members of the solicited advisory committee might also be co-opted on the Working Group and a Working Group co-Chair may be appointed from among members of this other advisory committee. In this case, the selection of Working Group members will equally involve the Chair and secretariat of the solicited advisory committee.

Working Group members will not be remunerated for their participation in the Working Group; however, reasonable expenses such as travel expenses incurred by attendance at Working Group meetings, SAGE meetings or related meetings will be compensated by WHO.

Working Group Process

Working Groups, with support of the WHO Secretariat will perform or coordinate, systematic assessment of the evidence such as analysis of data addressing efficacy, effectiveness, safety, feasibility, and economic aspects of immunization policy to address questions developed by the Working Group in order to propose appropriate vaccine policy recommendations. This is done in accordance with the process for evidence –review and development of recommendations by SAGE as available at http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf?ua=1. SAGE uses the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process for the review of evidence. The Working Group will be expected to define the questions to inform the recommendations. It should identify critical questions for which an in-depth review/systematic review of the evidence is needed and determine important outcomes. In developing proposed recommendations the Working Group should complete an evidence-to-recommendation table and systematically consider the following criteria: balance of benefits and harms of the intervention, resource use and value for money, equity impacts, feasibility, acceptability, values and preferences, and other relevant considerations. Recommendations should be based on GRADing of evidence. Only when not appropriate (and as per criteria stated in the Guidance for the development of evidence-based vaccine related recommendations) the group may opt to develop Good Practice Statements.

All proposed recommendation and comprehensive evidence in support of recommendations including GRADE tables and evidence to decision tables should be presented to SAGE.

SAGE Working Groups are not allowed to render consensus advice or recommendations directly to the WHO Director-General. SAGE Working Group Chairs, other Working Group representatives, or the Working Groups per se are not empowered to speak on behalf of SAGE. Rather, they are utilized by SAGE to gather and organize information upon which SAGE can deliberate and act. Thus, while SAGE Working Groups can and should examine an area in detail and define the issues, including developing options for recommendations, the actual processes of group deliberation terminating in development of group consensus and recommendations must occur in the public forum of SAGE meetings by SAGE. If the Working Group cannot reach consensus then the diverging views will be reflected in the background document or Working Group report presented to SAGE. Such documents will be publicly posted on the SAGE website as soon as the SAGE meeting is over.

Effective communication and a strong working collaboration between the Working Group Chair, Lead WHO staff and the Working Group members are significant determinants of the effectiveness of a Working Group. Draft minutes of Working Group in person meetings or conference calls are produced. As soon as the minutes are approved by the Working Group, they are made available to SAGE members on a protected web workspace. Depending on the Working Group, minutes may be produced by the Secretariat or a Working Group member may be asked to serve as rapporteur. Minutes are not publicly available and are only publicly shared in the context of a SAGE session when included in the background documents.

With the lead WHO Staff, the Chair of the Working Group develops a plan for routine operations of the group. Working Groups accomplish most of their work through teleconferences. A set day and time for routine monthly teleconferences may be established, in order to allow standing teleconferences to be arranged and Working Group members to anticipate and reserve time for these teleconferences. The frequency of Working Group teleconferences may be changed depending on the urgency of issues being considered by the group and the amount of preparatory work needed prior to a topic being brought up for plenary discussion and decision making at SAGE. Some Working Groups may more effectively achieve their purpose through exchange of e-mail communications with intermittent teleconferences. WHO establishes the telephone bridge for teleconferences and ensures free access that telephone charges are not impacted to Working Group members.

In-person meetings of Working Groups may facilitate the proceedings of the group and Working Groups are expected to have at least one face-to-face meeting. If a Working Group is planning to conclude its proceedings at a given face-to-face meeting, this meeting should be held at least one month in advance of the SAGE meeting during which the Working Group is expected to report to SAGE to allow for sufficient time to draft the background materials and proposed recommendations. These face-to-face meetings are normally held in Geneva but they may also be held in different locations if this minimizes cost and facilitates participation of Working Group members and necessary experts.

Individuals other than Working Group members and the Secretariat may participate in Working Group meetings only if their contribution is required by the Working Group. These may include organization representatives, industry representatives/experts, public health officials, faculty staff of academic institutions or other experts. These experts are excluded from any discussions and

deliberations within the Working Group and are solely invited to provide specific requested information on a predefined topic. Observers are not allowed to attend Working Group proceedings.

Working Groups are terminated after completion of the TOR and reporting to SAGE unless SAGE asks for additional work. Working Group focused on the development of recommendations on vaccine use may only be closed after the WHO position paper is published following the issuance of recommendations by SAGE. Working Group members will be asked to contribute to the peer-review of the document prior to publication and might be asked to help address reviewer's comments.

Working Groups are encouraged to submit publications of the reviews of the scientific evidence to peer-review journals. This could be done before or after the SAGE meetings. If published before the SAGE meeting, the publications should reflect the scientific evidence only and not pre-empt the view of SAGE with stating the proposed recommendations and if published after the SAGE meeting should reference the SAGE report.

Management of Conflict of Interest

The value and impact of SAGE recommendations and WHO policy recommendations are critically dependent upon public trust in the integrity of the process. Reported interests are assessed and managed according to SAGE procedures. A summary of the declared interests is publicly posted on the SAGE website in conjunction with the Working Group's TORs and composition (http://www.who.int/immunization/sage/working_mechanisms/en/). Members are expected to proactively inform WHO on any change in relevant interests. These will then be thoroughly assessed by the Working Group Chair, the SAGE Executive secretary as well as the Chair of SAGE. In case of a constituted conflict of interest, the selection panel will meet (see above) to determine a replacement. Should the declared change not result in a conflict of interest, the Working Group member will be able to remain on the Working Group. In both cases, the posted summary will be updated accordingly.

CURRENT SAGE WORKING GROUPS

Disclaimer: this list includes the current working groups and their active members. These working groups are listed in the order in which they were established. For the complete history of current and previous working groups and their membership from inception, please visit the SAGE website (http://www.who.int/immunization/sage/working_mechanisms/en/).

1. SAGE working group on polio (established August 2008)

Terms of Reference

1. Prepare SAGE for the development of comprehensive policy guidance on the use of IPV in the post-eradication era in low and middle income settings, including by:
 - a. Reviewing long-term Polio Risks & Risk Management Strategies: reviewing the long-term risks associated with live polioviruses after wild polio transmission globally, and reviewing the range of strategies for mitigating those risks in low-income settings (e.g. coordinated OPV cessation, mOPV stockpiles and response mechanism).
 - b. Assessing Current & Future IPV Products: reviewing the existing range of IPV products, in terms of supply capacity, production cost, price, presentations, etc, and their appropriateness and suitability for low-income settings, particularly sub-Saharan Africa; and studying the IPV 'pipeline' and its implications for post-eradication IPV use in terms of potential new products (e.g. Sabin-IPV, adjuvanted-IPV, fractional dose IPV), production costs, and prices.
 - c. Establishing Potential IPV Policies & Implications: establishing the range of IPV vaccination schedule options that could be utilized in a post-eradication world, given the difference in polio immunization objectives and polio risks compared with a polio-endemic world; and identifying and characterizing the programmatic implications, economics and opportunity costs of those policy options, for both IPV stand-alone and combination formulations, in low-income settings and particularly sub-Saharan Africa;
 - d. Identifying and prioritizing knowledge gaps that should be addressed to facilitate SAGE decision-making on the role(s) and options for IPV use in the post-eradication era in low-income settings.
2. Propose key recommendations to SAGE for updating the 2003 position paper on IPV and consolidating it with other relevant documents (including the 2006 supplement to the IPV position paper) into one vaccine position paper on routine polio immunization covering both IPV and OPV and giving consideration to the ongoing polio eradication efforts.
3. Advise SAGE on technical guidance to WHO and the GPEI for the development and finalization of the overall polio eradication 'endgame strategy' to reduce long-term risks associated with OPV and to accelerate wild poliovirus eradication, including:
 - a. Policy and programmatic options for the use of different OPV formulations and IPV delivery options, and
 - b. Strategy and priorities in the related areas of outbreak response, surveillance, containment, risk assessment (esp. Vaccine Derived Polio Viruses - VDPVs), research and product development, and vaccine supply.

Composition

SAGE Members

- Yagob Al-Mazrou: Health Services Council, Saudi Arabia. (Chair of the Working Group from September 2015)
- Ilesh Jani: National Institute for Health, Mozambique. (Member of the Working Group from October 2016)

Experts

- Elizabeth Miller: Public Health England, United Kingdom. (Chair of the Working Group until February 2014 and SAGE member until November 2013)
- Jacob John: Christian Medical College, India.
- Jeffery Mphahlele: South African Medical Research Council, South Africa. (Member of the Working Group from October 2016)
- Khalequzzaman Zaman: International Centre for Diarrhoeal Disease Research, Bangladesh. (Member of the Working Group from October 2016)
- Kimberley Thompson: Harvard University, United States of America.
- Nick Grassly: Imperial College, United Kingdom.
- Peter Figueroa: University of the West Indies, Jamaica. (Chair of the Working Group until August 2015 and SAGE member until April 2015)
- Walter Dowdle: Task Force for Child Health, United States of America.
- Walter Orenstein: Emory University, United States of America.
- Youngmee Jee: Korean Centre for Disease Control and Prevention, Republic of Korea. (Member of the Working Group from October 2016)
- Zulfiqar Bhutta: The Aga Khan University, Pakistan. (Member of the Working Group from Nov 2012 and SAGE member until April 2015)

2. SAGE working group on measles and rubella vaccines (established November 2011)

Terms of Reference

1. Review progress towards 2015 global measles control targets and regional measles and rubella elimination goals.
2. Prepare for regular updates and review by SAGE on progress and challenges in achieving existing measles and rubella control targets and propose necessary updating of current WHO recommendations on vaccine use (including outbreak response immunization) and surveillance strategies.
3. Identify gaps in essential evidence and programme barriers to achieving measles and rubella/CRS elimination targets and present SAGE with proposed areas for operational or basic science research. The working group will liaise with SAGE Sub-Committees (i.e., QUIVER and IPAC) to address relevant quantitative issues as well as those related to immunization practices.
4. Advise SAGE on the appropriate timing for establishing target dates for global eradication of measles and global control or eradication targets for rubella and/or CRS.

Composition

SAGE Members

- Nikki Turner: University of Auckland, New Zealand. (Chair of the Working Group from October 2016)
- Ilesh Jani: National Institute for Health, Mozambique. (Member of the Working Group from October 2015)

Experts

- David Durrheim: Hunter New England Area Health Service, Australia. (SAGE member until April 2012)
- Helen Rees: University of Witwatersrand, South Africa. (former SAGE Chair 2010 - 2013)
- Hyam Bashour: retired (former Damascus University, Syrian Arab Republic). (SAGE member until April 2011)
- Narendra Arora: International Clinical Epidemiology Network, India. (Chair of the Working Group until September 2016 and SAGE member until April 2016)
- Natasha Crowcroft: Public Health Ontario, Canada.
- Peter Figueroa: University of the West Indies, Jamaica. (Chair of Working Group until August 2015 and SAGE member until April 2015)
- Susan Reef: Centers for Disease Control and Prevention, United States of America.
- William Moss: Johns Hopkins University, United States of America.

3. SAGE Working Group on the Decade of Vaccines (established March 2013)

Terms of Reference

The SAGE Working Group (WG) will facilitate a yearly SAGE independent review of the implementation of the Decade of Vaccines' Global Vaccine Action Plan (GVAP) and assessment of progress. Specifically, the WG will:

1. Review the quality of the data on the GVAP indicators and make recommendations on changes to the formulation of the indicators, operational definitions and/or the processes for data collection;
2. Independently evaluate and document progress towards each of the 6 GVAP Strategic Objectives and towards the achievement of the Decade of Vaccines Goals (2011-2020), using the GVAP Monitoring & Evaluation / Accountability Framework;
3. Identify successes, challenges and areas where additional efforts or corrective actions by countries, regions, partners, donor agencies or other parties, are needed;
4. Identify and document best practices;
5. Prepare the GVAP implementation annual report to be presented to the SAGE, and thereafter, with SAGE inputs, be submitted for discussion to the WHO January EB meeting, to the WHA and the independent Expert Review Group (IERG) for the UN Secretary General's Global Strategy for Women's and Children's Health.

In its review the WG should take a broad perspective, encompassing the general environment, including the health system context.

Composition

SAGE Members

- Narendra Arora: International Clinical Epidemiology Network, India. (Chair of the Working Group and SAGE member until April 2016)
- Alejandro Cravioto: Global Evaluative Sciences, United States of America.
- Yagob Al-Mazrou: Health Services Council, Saudi Arabia.

Experts

- Amani Mahmoud Mustafa: The Carter Center, Sudan.

- Budihardja Singgih: Australia Indonesia Partnership for Health Systems Strengthening, Indonesia. (Member of the Working Group from May 2016)
- David Salisbury: Centre on Global Health Security, United Kingdom. (former SAGE Chair 2005 - 2010)
- Helen Rees: University of Witwatersrand, South Africa. (former SAGE Chair 2010 - 2013)
- Jon Kim Andrus: Sabin Vaccine Institute, United States of America. (Member of the Working Group from May 2016)
- Marie-Yvette Madrid: Independent Consultant, Switzerland
- Oleru Huda Abason: Parliament of Uganda, Uganda. (Member of the Working Group from May 2016)
- Qinjian Zhao: Xiamen University, China. (Member of the Working Group from May 2016)
- Rebecca Martin: Centers for Disease Control and Prevention, United States of America.
- Susan Elden: Department for International Development, United Kingdom. (Member of the Working Group from May 2016)

4. SAGE Working Group on Ebola Vaccines and Vaccination (established November 2014)

Terms of Reference

The Strategic Advisory Group of Experts (SAGE) on Immunization Working Group is exceptionally established with an urgent program of work to facilitate a SAGE review of available evidence and advice to WHO on the potential post-licensure use of the Ebola vaccines in order to mitigate the public health impact of the disease and possibly curtail the ongoing epidemic, as well as to prevent or reduce the risk of spread of disease in the future. The Working Group will consult with the Task Force for Immunization for the African region to get their inputs into the operationalization of immunization delivery and consolidate the feedback into a report to SAGE with recommendations on potential strategies for the deployment of vaccines.

In order to facilitate the review, the Working Group will provide technical advice and support to the WHO secretariat by:

1. Reviewing the essential evidence required for making policy recommendations and on strategies for deployment of vaccines.
2. Reviewing the available epidemiological data to define the risk of disease and mortality in different population groups in order to allow prioritization of vaccination.
3. Reviewing the evidence, as it becomes available, on the safety, and efficacy of candidate vaccines, including the optimal vaccination schedules to be used for each vaccine.
4. Reviewing the data on the projected impact of different vaccination strategies generated by mathematical models.
5. Reviewing the synthesis of the above data for presentation to SAGE and in drafting recommendations for consideration by SAGE.
6. Reviewing the projections of vaccine supply to inform recommendations on the deployment of vaccines.

Composition

SAGE Members

- Fred Were: University of Nairobi, Kenya. (Co-Chair of the Working Group from April 2016)
- Charles Wiysonge: Stellenbosch University, South Africa
- Kate O'Brien: Johns Hopkins University, United States of America.

Experts

- Helen Rees: University of Witwatersrand, South Africa. (Co-Chair of the Working Group and former SAGE Chair 2010 - 2013)
- Ann Kelly: University of Exeter, United Kingdom.
- Chris Ockenhouse: PATH, United States of America.
- David Durrheim: Hunter New England Area Health Service, Australia. (SAGE member until April 2012)
- Diop Ndack: University Cheikh Anta Diop, Senegal.
- George Bonsu: Ministry of Health, Ghana.
- Jean-Paul Jemmy: Médecins Sans Frontières, Belgium.
- Jesse Goodman: Georgetown University, United States of America.
- Keymanthri Moodley: Stellenbosch University, South Africa.
- Nick Andrews: Public Health England, United Kingdom.
- Oyewale Tomori: Redeemer's University, Nigeria. (Co-Chair of the Working Group until March 2016 and SAGE member until April 2015)
- Cesar Velasco Muñoz: Hospital Clínico Lozano Blesa, Spain.

Ex-Officio members

- Chris Morgan: Chair of WHO Immunization Practices Advisory Committee (IPAC).
- Ellwyn Griffiths: Chair of WHO Expert Committee on Biological Standardization (ECBS).
- Robert Breiman: Chair of WHO Immunization and Vaccines Related Implementation Research Advisory committee (IVIR-AC).

- Robert Pless: Chair of WHO Global Advisory Committee on Vaccine Safety (GACVS). (Member of the Working Group from December 2015)

5. SAGE Working Group on maternal and neonatal tetanus elimination and broader tetanus prevention (established October 2015)

Terms of reference

1. To critically look into the reasons why the previously set elimination target dates have been missed and how to address these.
2. To propose a process for “resetting” the MNT elimination agenda in a sustainable manner.
3. To look into the risk of tetanus in other age groups and genders and propose how this can be comprehensively addressed.
4. To discuss the role of strengthening integration of Tetanus Toxoid containing vaccines into antenatal care and other delivery platforms (e.g. school-based vaccination) and strategies to ensure clean deliveries as part of the “reset” agenda.
5. To review experiences especially from the countries that attained MNT elimination with limited or no campaigns.
6. To think out of the box including on how to capitalize on infant routine immunization and on the strategies that have to be adapted to the local context, like conflict affected areas, and linkages with other programmes targeting the poor and marginalized groups.
7. To discuss the learning agenda from MNT as pathfinder for further maternal vaccines.

Composition

SAGE members

- Kari Johansen: European Centre for Disease Prevention and Control, Sweden. (Chair of the Working Group)
- Charles Wiysonge: Stellenbosch University, South Africa.
- Jaleela Sayed Jawad: Ministry of Health, Bahrain.

Experts

- Alexis Ntabona: ExpandNET, Democratic Republic of the Congo.
- Ardi Kaptiningsih: retired (former WHO Western Pacific Regional Office, Philippines).
- Bradford Gessner: Agence de Médecine Préventive, France.
- Elizabeth Mason: retired (former WHO Child and Adolescent Health, Switzerland).
- Elizabeth Miller: Public Health England, United Kingdom. (SAGE member until November 2013)
- Rakesh Kumar: Ministry of Health & Family Welfare, India.
- Robert Steinglass: John Snow Inc., United States of America.
- Tony Nelson: The Chinese University of Hong Kong, China.

6. SAGE Working Group on Oral Cholera Vaccines (established November 2015)

Terms of reference

1. To analyse the results of the most recent research and M&E activities implemented during OCV campaigns since the 2010 WHO recommendation with a particular focus on communities’ acceptability, safety of OCV, vaccine effectiveness in various settings, cost analysis, impact on cholera transmission in endemic and epidemic settings
2. To review evidence and propose recommendations for use of OCV in pregnant and lactating women
3. To review evidence and propose recommendations for use of OCV in travelers
4. To review evidence and propose updated recommendations for vaccination strategies (Controlled Temperature Chain, single dose, self-administration, administration with other vaccines, ring vaccination)
5. To critically discuss the 2010 WHO recommendations on OCV use and propose potential adjustments/revisions for endemic settings (“hotspots”), during humanitarian emergencies and during outbreaks
6. To consider the perspectives of development of OCV and discuss the potential impact on the future of cholera control

Composition

SAGE Members

- Alejandro Cravioto: Global Evaluative Sciences, United States of America. (Chair of the Working Group)
- Firdausi Qadri: International Centre for Diarrhoeal Disease Research, Bangladesh.
- Jaleela Sayed Jawad: Ministry of Health, Bahrain.

Experts

- Asma Yaroh Gali: Ministry of Public Health, Niger.

- Cynthia Sema: National Institute for Health, Mozambique.
- Dang Duc Anh: National Institute of Hygiene and Epidemiology, Viet Nam.
- Dipika Sur: retired (former National Institute of Cholera and Enteric Diseases, India).
- Francis Javier Alcalde Luquero: Johns Hopkins University, United States of America.
- Louise Ivers: Harvard University, United States of America.
- Rebecca Grais: Epicentre, France.
- Thomas Wierzba: PATH, United States of America.

7. SAGE Working Group on Typhoid Vaccines (established March 2016)

Terms of reference

The Working Group will be requested to review the scientific evidence and relevant programmatic considerations to formulate updated recommendations on the use of typhoid vaccines, with a focus on typhoid conjugate vaccines (TCVs). The proposed recommendations will be submitted for consideration by SAGE for revision of the global policy on typhoid vaccine use, and for subsequent updating of the WHO Position Paper on typhoid vaccines (2010). Publication of an updated position paper on typhoid vaccines is tentatively scheduled for 2018.

Specifically, the Working Group will review evidence on:

1. The epidemiology and burden of disease caused by *S. Typhi* and implications for control, including risk factors, diagnostics and other issues related to typhoid surveillance and better understanding of the disease epidemiology;
2. Trends in antimicrobial resistance and implications for the control of typhoid fever;
3. The safety, immunogenicity profile, effectiveness, duration of protection and indications for booster doses of TCVs in the context of existing typhoid vaccines;
4. The optimum schedule and age of administration as well as delivery strategies for typhoid vaccines; including administration of TCVs to children under 2 years of age;
5. The economic burden of typhoid fever and cost-effectiveness of vaccination (including vaccination in the context of other control strategies); and
6. Considerations for the use of typhoid vaccines in endemic as well as epidemic or emergency settings.

Composition

SAGE Members

- Ilesh Jani: National Institute for Health, Mozambique. (Chair of the Working Group)
- Kari Johansen: European Centre for Disease Prevention and Control, Sweden.

Experts

- Christopher Parry: London School of Hygiene and Tropical Medicine, United Kingdom.
- Dafrossa Lyimo: Ministry of Health, United Republic of Tanzania.
- Dipika Sur: retired (former National Institute of Cholera and Enteric Diseases, India).
- Florian Marks: International Vaccine Institute, Republic of Korea.
- John A. Crump: University of Otago, New Zealand.
- Mark Miller: National Institutes of Health, United States of America.
- Myron Levine: University of Maryland, United States of America.
- Narendra Arora: International Clinical Epidemiology Network, India. (SAGE member until April 2016)
- Richard Strugnell: University of Melbourne, Australia.
- Zulfiqar Bhutta: The Aga Khan University, Pakistan. (SAGE member until April 2015)

8. SAGE Working Group on rabies vaccines and rabies immunoglobulins (established July 2016)

Terms of reference

The Working Group is requested to review the scientific evidence and relevant programmatic considerations, to formulate proposed recommendations on the use of rabies vaccines and immunoglobulins.

Specifically the Working Group will be asked to review the following elements:

1. Assess evidence and country practices in the use of human rabies vaccine and rabies immunoglobulins (RIG), including that of targeted vaccination of high risk communities in rural settings;
2. Review the new evidence on the need for pre-exposure prophylaxis (PREP) booster doses and the cost-effectiveness of the interventions;
3. Assess the most recent evidence on the potential shortening of post-exposure prophylaxis (PEP) schedules and new regimens;
4. Review the evidence and revisit the current WHO position for RIG and monoclonal antibody use with the view to improve access to care and increase public health impact;

5. Assess the implementation and evidence of the current recommendation on intradermal use of cell culture-derived vaccines (CCV);
6. Economic burden of rabies and cost-effectiveness of vaccination as well as modelling data should be assessed to inform rabies vaccination strategies (including vaccination in the context of other control strategies);
7. Consideration should be given to new vaccines in different phases of clinical trials or in the process of obtaining WHO prequalification and/or national market authorization by mid/end 2016.

Composition

SAGE Members

- Kate O'Brien: Johns Hopkins University, United States of America. (Chair of the Working Group)
- Terry Nolan: University of Melbourne, Australia.

Experts

- Ahmed Be-Nazir: National Institute of Preventative and Social Medicine, Bangladesh.
- Arnaud Tarantola: Institut Pasteur, Cambodia.
- Deborah Briggs: Kansas State University, United States of America.
- Gade Sampath: Institute of Preventative Medicine, India.
- Henry Wilde: Chulalongkorn University, Thailand.
- Lucille Blumberg: National Institute for Communicable Diseases, South Africa.
- Luzia Queiroz: University of Sao Paulo State, Brazil.
- Mary Warrell: University of Oxford, United Kingdom.
- Mathurin Cyrille Tejiokem: Centre Pasteur, Cameroon.
- Naseem Salahuddin: The Indus Hospital, Pakistan.

9. SAGE Working Group on the use of bacille Calmette-Guérin vaccine (under establishment)

Terms of Reference

The Working Group will be requested to review the scientific evidence and relevant programmatic considerations to formulate proposed recommendations on the use of BCG vaccines for consideration by SAGE to inform a revision of the global policy on the use of BCG, and for subsequent updating of the WHO Position Paper on BCG and related materials.

Specifically the Working Group will be asked to review the following elements:

1. Country practices in the use of BCG including that of targeted vaccination in low TB prevalence countries as well as the threshold applied to decide on stopping vaccination;
2. TB epidemiology as well as the epidemiology of leprosy;
3. Trends in antibiotic resistance and their implications for BCG use;
4. The safety, effectiveness, and duration of protection afforded by administration of BCG (in a strain specific analysis) in different age groups and according to HIV status and for different outcomes (i.e. death, pulmonary disease and infection) and assessment of the effect of booster doses (including a comparison of the effect of BCG booster/revaccination with alternative protection e.g. isoniazid preventive therapy);
5. The effect of BCG co-administration with other vaccines administered at birth (OPV, hepatitis B) or later (e.g. co-administration with DTP containing and specifically pentavalent vaccine);
6. The economic burden of TB and cost-effectiveness of vaccination as well as modelling data to inform BCG vaccination strategies (including vaccination in the context of other control strategies);
7. The potential role of BCG in the control of leprosy.

In addition the Working Group will be briefed on the TB vaccine candidates development status, and will consider BCG improvement strategies that may have implications for beneficial non-specific vaccine effects of the current BCG.

The vaccine has several non-specific effects which should be discussed but which should not be the immediate focus of the Working Group since this issue of non-specific effects is being address by the Immunization and Vaccines-Related Implementation Research Advisory Committee (IVIR-AC).

10. SAGE Working Group on pneumococcal conjugate vaccine (under establishment)

Terms of Reference

1. Review and summarize the measured and modelled evidence on PCV immunogenicity and impact (direct and indirect) on carriage, disease, and mortality with respect to the following questions/issues:
 - a. Effectiveness and/or impact of different schedules and strategies for PCV use in industrialized and developing countries;
 - b. Preference of 2p+1 or 3p+0 schedule for current or future impact
 - c. Choice of PCV products;

- d. Catch-up vaccination of infants and/or older age groups during PCV introduction;
 - e. Maximize herd protection;
 - f. Optimize duration of protection.
2. Propose to SAGE recommendations on optimal PCV use related to the above listed questions and issues in order to revisit the 2012 WHO PCV position paper.
3. Identify and prioritize knowledge gaps and critical questions to prepare a concrete scope of work with a proposed timeline for future PCV working group activities. The following questions/issues will likely be included:
 - a. Serotype replacement in the era of extended valency conjugate vaccines;
 - b. Options for optimal PCV use in the future, including in settings of near-elimination levels of vaccine serotype disease;
 - c. PCV use in adults, including the elderly;
 - d. Incremental benefit of the polysaccharide vaccine in adults in era of PCV use.
4. Provide SAGE with summaries and analyses needed to support its discussion and recommendation process.

**Strategic Advisory Group of Experts on Immunization meeting
18 - 20 October 2016
Centre International de Conférences, (CICG), Geneva, Switzerland**

Provisional list of participants as of 27 September 2016

SAGE Members

<p>Abramson, Jon SAGE Chair Professor, Department of Pediatrics Wake Forest Baptist Health 27104 Winston-Salem United States of America</p>
<p>Al-Mazrou, Yagob Yousef Secretary General Saudi Health Council 3161-13315 Riyadh Saudi Arabia</p>
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better preparedness, leading to better detection. Nigeria has learnt from Ebola virus disease and has built better capacity to detect emerging outbreaks, including raising awareness of disease threats through stronger community engagement.

Molecular dating suggests that Lassa virus has been circulating in Nigeria for over a thousand years, and in some other West African countries for hundreds of years. This year, genetic sequencing of the virus causing infections in Togo showed that this virus and one circulating in neighbouring Benin represent a new lineage of the Lassa virus. The animal reservoir of the virus is a rat species (*Mastomys natalensis*); the Lassa virus is most commonly transmitted from rats to humans (85–95 % of cases) through contact with rat faeces and urine.

The larger and wider outbreaks observed in West Africa may be due to increasing urbanization and to climatic conditions favouring the rat. West Africa has enjoyed good rainfall since November 2015, possibly due to the El Niño phenomenon, which has led to good crop yields and plentiful food for rodents.

Human to human transmission occurs in a small percentage of cases but usually only in hospitals or mortuaries. Good infection prevention and control practices in health-care facilities are key to preventing the spread of epidemic-prone viruses.

Tips

The best ways of preventing human infection are to reduce the rat population and avoid any contact with rat excreta. To avoid contact with rat excreta, people are advised to always wash their hands before handling and eating food; store food in covered containers; cook all foods thoroughly; and discourage rats by clearing away any rubbish in or around the house and keeping a cat.

Further information is available at:

<http://www.who.int/csr/disease/epidemic-focus/en/>
http://www.who.int/csr/don/archive/disease/lassa_fever/en/
<http://www.who.int/mediacentre/factsheets/fs179/en/> ■

Meeting of the Strategic Advisory Group of Experts on immunization, April 2016– conclusions and recommendations

The Strategic Advisory Group of Experts (SAGE) on immunization¹ met on 12–14 April 2016. This report summarizes the discussions, conclusions and recommendations.²

¹ See <http://www.who.int/immunization/sage/en/index.html>; accessed May 2016.

² Presentations and background materials used for the SAGE meeting together with the list of SAGE members and summarized declarations of interests are available at <http://www.who.int/immunization/sage/meetings/2016/april/en/index.html>; accessed May 2016.

ration, entraînant une amélioration de la détection. Le Nigéria a tiré les leçons de la maladie à virus Ebola et a amélioré ses capacités de détection des flambées émergentes, notamment par la sensibilisation aux menaces de maladies grâce à un plus fort engagement des communautés.

Les données moléculaires indiquent que le virus de Lassa circule au Nigéria depuis plus d'un millier d'années et dans d'autres pays d'Afrique de l'Ouest depuis plusieurs siècles. Cette année, le séquençage génétique du virus à l'origine des infections au Togo a montré que celui-ci ainsi qu'un autre virus circulant au Bénin voisin appartiennent à une nouvelle lignée. Le réservoir chez l'animal est un rat de l'espèce *Mastomys natalensis* et le virus de Lassa se transmet le plus souvent du rat à l'être humain (dans 85–95% des cas) par contact avec les déjections ou les urines du rongeur.

Les flambées plus importantes et plus étendues observées en Afrique de l'Ouest pourraient être dues à l'urbanisation accrue et aux conditions climatiques favorables au rat. L'Afrique de l'Ouest a bénéficié de précipitations abondantes depuis novembre 2015, peut-être à cause du phénomène El Niño, ce qui a permis de bons rendements des cultures et donné de la nourriture en abondance aux rongeurs.

On observe la transmission interhumaine dans une petite proportion des cas, mais en général seulement dans les hôpitaux ou les morgues. De bonnes pratiques de lutte contre les infections dans les établissements de santé sont essentielles pour éviter la propagation des virus à potentiel épidémique.

Conseils

Le meilleur moyen d'éviter l'infection chez l'être humain consiste à réduire les populations de rats et à éviter tout contact avec leurs déjections. Pour éviter d'être en contact avec des excréments de rat, il est conseillé de toujours se laver les mains avant de manipuler ou de consommer de la nourriture, de conserver les denrées dans des récipients fermés avec un couvercle, de cuire suffisamment tous les aliments et de repousser les rats en enlevant tous les débris à l'intérieur ou autour des maisons et en ayant un chat.

Pour plus d'informations:

<http://www.who.int/csr/disease/epidemic-focus/en/>
http://www.who.int/csr/don/archive/disease/lassa_fever/fr/
<http://www.who.int/mediacentre/factsheets/fs179/fr/> ■

Réunion du Groupe stratégique consultatif d'experts sur la vaccination, avril 2016 – conclusions et recommandations

Le Groupe stratégique consultatif d'experts (SAGE) sur la vaccination¹ s'est réuni du 12 au 14 avril 2016. Le présent rapport résume les discussions, conclusions et recommandations auxquelles il est parvenu.²

¹ Voir <http://www.who.int/immunization/sage/fr/index.html>; consulté en mai 2016.

² Les communications et les documents de travail utilisés pour la réunion du SAGE, ainsi que la liste des membres du SAGE et une synthèse de leurs déclarations d'intérêts sont disponibles à l'adresse: <http://www.who.int/immunization/sage/meetings/2016/april/en/index.html>; consulté en mai 2016.

Report from the WHO Department of Immunization, Vaccines and Biologicals

Good progress was reported on the development and implementation of regional vaccine action plans, while recognizing the need for a much stronger role of the immunization Regional Technical Advisory Groups (RTAGs) in oversight of the regional programmes to ensure accountability. RTAGs were encouraged to provide specific guidance to National Immunization Technical Advisory Groups (NITAGs) and programme managers to enable countries to reach their immunization goals.

The WHO core functions in the field of immunization outlined in the “WHO Vision and Mission” were emphasized, as well as the transformational outcomes agreed during a retreat in Evian, France, March 2016, in which WHO staff from least-performing countries, the Regional Offices and Headquarters participated. The report called for a stronger voice of the immunization community in communicating the benefits of vaccination to audiences beyond their primary focus, such as those dealing with reproductive, maternal, neonatal and child health, and health system strengthening.

At global level, 2016 was an important year for the Global Vaccine Action Plan (GVAP) and Decade of Vaccines. The GVAP mid-term review findings, lessons learnt and priorities for 2017–2020 will be included in the next SAGE report. Approval of a vaccination coverage indicator under the child mortality target of the Sustainable Development Goals (SDGs) has not yet been obtained. SAGE urged WHO and countries to request an aspirational immunization indicator under the SDGs.

Ensuring and sustaining immunization services disrupted by humanitarian crises is an ongoing concern. Despite major challenges, successful activities had been implemented in crisis-affected countries in the Eastern Mediterranean Region (EMR). SAGE expressed appreciation of these activities and stressed the need for continuous efforts in strengthening vaccination in humanitarian crises including further updating of field vaccination guides.

The WHO R&D Blueprint was highlighted. It aims at developing and implementing a roadmap for R&D preparedness for priority pathogens, and enabling roll-out of efficient emergency R&D responses. In this context, WHO is developing target product profiles for potential Zika virus vaccines.

SAGE applauded the latest developments and proposed that experience with Ebola vaccine development be used to guide the development of vaccines against other priority emerging pathogens.

Promising data are emerging from the Ebola vaccine trials. Pending regulatory approval, WHO is developing

Rapport du Département Vaccination, vaccins et produits biologiques de l'OMS

Le rapport a fait état des progrès sensibles réalisés dans l'élaboration et la mise en œuvre des plans d'action régionaux pour les vaccins, tout en soulignant que les groupes consultatifs techniques régionaux sur la vaccination (RTAG) doivent jouer un rôle beaucoup plus actif dans la surveillance des programmes régionaux pour veiller à la responsabilisation de toutes les parties prenantes. Les RTAG ont été invités à fournir des orientations précises aux groupes consultatifs techniques nationaux sur la vaccination et aux administrateurs des programmes pour les aider à atteindre les objectifs de vaccination de leur pays.

Le rapport a mis l'accent sur les principales fonctions de l'OMS en matière de vaccination, telles qu'énoncées dans la vision et la mission de l'OMS, et a présenté les conclusions innovantes d'un séminaire de réflexion organisé à Évian (France) en mars 2016, réunissant du personnel de l'OMS venant des pays les moins performants, ainsi que des bureaux régionaux et du Siège. Le rapport a appelé la communauté de la vaccination à mieux faire entendre sa voix en exposant les avantages de la vaccination à des groupes ne se limitant pas à son public cible principal, notamment parmi les personnes intervenant dans la santé reproductive, maternelle, néonatale et infantile ou dans le renforcement des systèmes sanitaires.

Au niveau mondial, l'année 2016 a été importante pour le Plan d'action mondial pour les vaccins (GVAP) et la Décennie de la vaccination. Les résultats de l'évaluation à mi-parcours du GVAP, les enseignements tirés et les priorités pour 2017-2020 figureront dans le prochain rapport du SAGE. Aucun indicateur de couverture vaccinale n'a encore été approuvé dans le cadre de la cible des objectifs de développement durable (ODD) relative à la mortalité de l'enfant. Le SAGE a vivement encouragé l'OMS et les pays à demander que soit défini un indicateur de vaccination idéal au titre des ODD.

La nécessité d'assurer des services de vaccination durables dans des contextes où ces derniers ont été perturbés par des crises humanitaires demeure une source de préoccupation. Malgré d'importants obstacles, certaines activités ont pu être menées avec succès dans des pays en situation de crise de la Région de la Méditerranée orientale. Le SAGE s'est félicité de ces actions et a souligné la nécessité de consacrer des efforts soutenus au renforcement de la vaccination lors des crises humanitaires, notamment par une mise à jour des guides pratiques de vaccination.

Le rapport a souligné l'importance du schéma directeur de l'OMS en matière de recherche développement, qui vise à élaborer et mettre en œuvre une feuille de route pour la préparation des activités de R&D contre les agents pathogènes prioritaires et à permettre une intervention d'urgence efficace en matière de R&D. Dans ce cadre, l'OMS travaille actuellement à la définition des profils cibles de produits applicables aux vaccins potentiels contre le virus Zika.

Le SAGE a salué ces dernières évolutions et proposé que l'expérience acquise dans le cadre de la mise au point d'un vaccin contre Ebola soit utilisée pour orienter le développement de vaccins contre d'autres agents pathogènes émergents prioritaires.

Les essais sur les vaccins contre le virus Ebola ont donné des résultats encourageants. En attendant que ces vaccins obtiennent

a country-based “Expanded Access Brigade” to facilitate use until an Ebola vaccine is licensed.

Following the October 2015 recommendations from SAGE and the Malaria Policy Advisory Committee, a public call for expression of interest triggered responses from 10 countries to serve as settings for pilot implementation of RTS,S malaria vaccine; selection of countries to host these pilot projects is currently ongoing.

Developments in the field of vaccine administration via microarray patches were outlined. WHO is working with developers, regulators, manufacturers and funders to clarify product development strategies.

The ongoing yellow fever (YF) outbreak in Angola and current YF vaccine supply constraints were noted with concern. As from 11 July 2016 an amendment to the International Health Regulations (IHR) will change the validity of the YF vaccination certificate from 10 years to the life of the person vaccinated, and will be legally binding for all Member States.

The European Region (EUR) reported substantial progress towards measles and rubella elimination. In early 2016, reported regional measles incidence was extremely low, with positive examples such as countries implementing national action plans for measles and rubella elimination. However, more work lies ahead and it will be important to maintain a focus on this objective. Also highlighted were the further increase in the number of established NITAGs and the EUR focus on people-centered service delivery. Areas of concern include (i) a reported death from diphtheria; (ii) resurgence of pertussis; and (iii) the low rate of vaccination in Ukraine. Vaccine supply issues and ensuring financial sustainability, particularly for middle-income countries, were also problematic.

In the Western Pacific Region (WPR), there has been steady progress towards the 8 goals of the regional framework for implementation of GVAP, notably through strengthening the NITAGs. Private sector provision of vaccines and strengthening of routine immunization are areas of focus for WPR and the RTAG. Setbacks include the re-importation of measles causing several outbreaks in the Region. The current outbreak of polio due to circulating vaccine-derived poliovirus (cVDPV) in the Lao People's Democratic Republic exemplifies the importance of enhancing the quality and equity of immunization services and addressing community demand as well as vaccine hesitancy issues.

In the Eastern Mediterranean Region (EMR), strengthening of routine immunization, particularly in hard-to-

l'approbation des autorités réglementaires, l'OMS s'emploie à mettre sur pied des «brigades d'accès élargi» dans les pays pour faciliter l'utilisation des vaccins contre Ebola en attente d'homologation.

Suite aux recommandations formulées par le SAGE et le Comité de pilotage de la politique de lutte antipaludique en octobre 2015, un appel à manifestation d'intérêt a été publié à l'intention des pays souhaitant servir de cadre à des projets pilotes de mise en œuvre du vaccin antipaludique RTS,S; 10 pays ont répondu à cet appel et la sélection est en cours.

Les dernières avancées en matière d'administration des vaccins par timbre à micro-aiguilles ont été présentées. En concertation avec les chercheurs, les autorités réglementaires, les fabricants et les bailleurs de fonds, l'OMS s'emploie à clarifier les stratégies de mise au point de ces produits.

Le SAGE a relevé avec préoccupation la persistance de la flambée de fièvre jaune en Angola, ainsi que les contraintes pesant actuellement sur l'approvisionnement en vaccin anti-amaril. À compter du 11 juillet 2016, un amendement du Règlement sanitaire international (RSI) modifiera la durée de validité du certificat de vaccination anti-amaril: au lieu de 10 ans, il restera valide pendant toute la durée de vie de la personne vaccinée. Cet amendement sera juridiquement contraignant pour tous les États Membres.

La Région européenne a considérablement progressé sur la voie de l'élimination de la rougeole et de la rubéole. Au début 2016, l'incidence régionale de la rougeole était extrêmement faible et des signes positifs étaient constatés, comme la mise en œuvre de plans d'action nationaux d'élimination de la rougeole et de la rubéole par les pays. Toutefois, il reste encore beaucoup à faire et les efforts consacrés à cet objectif ne doivent pas se relâcher. Il a également été fait état de l'augmentation du nombre de groupes consultatifs techniques nationaux sur la vaccination et de l'importance qu'accorde la Région européenne à la prestation de services centrés sur la personne. Des inquiétudes ont été exprimées sur les points suivants: i) la notification d'un décès imputable à la diphtérie; ii) une résurgence de la coqueluche; et iii) le faible taux de vaccination en Ukraine. Les problèmes d'approvisionnement en vaccins et les questions de viabilité financière, en particulier pour les pays à revenu intermédiaire, sont également sources de préoccupation.

La Région du Pacifique occidental a enregistré des progrès constants vers la réalisation des 8 objectifs du Cadre régional de mise en œuvre du Plan d'action mondial pour les vaccins, notamment grâce au renforcement des groupes consultatifs techniques nationaux sur la vaccination. La Région du Pacifique occidental et le groupe consultatif technique régional sur la vaccination prêtent une attention particulière à la fourniture de vaccins par le secteur privé et au renforcement de la vaccination systématique. La réimportation de la rougeole, à l'origine de plusieurs flambées dans la Région, figure parmi les difficultés rencontrées. La flambée actuelle de poliomyélite en République démocratique populaire lao, due au poliovirus circulant dérivé d'une souche vaccinale (PVDVc), illustre à quel point il est important d'améliorer la qualité et l'équité des services de vaccination, de stimuler la demande dans les communautés et de remédier aux problèmes de réticence à l'égard de la vaccination.

Dans la Région de la Méditerranée orientale, les efforts se concentrent sur le renforcement de la vaccination systématique,

reach and conflict-affected areas, is at the centre of work in the Region. Substantial progress has been achieved in re-implementing immunization services in northern Syria. Hepatitis B control is on track and verification is in progress. Vaccine shortages were a great concern and an impediment to implementing measles elimination activities. Neonatal tetanus was emphasised as a problem, with guidance awaited from SAGE to support advocacy for allocation of resources for implementation of related activities.

The Ministerial Conference on Immunization in February 2016, hosted by the WHO Regional Offices for Africa (AFRO) and the Eastern Mediterranean (EMRO) in collaboration with the African Union Commission, was a landmark in commitment to and promotion of immunization. Follow-up is ongoing to ensure accountability and implementation at country level.

The South-East Asia Region (SEAR) vaccine action plan, based on the 2014–2017 Strategic Plan, has been drafted and will be submitted to the RTAG for endorsement. NITAGs have now been established in all countries of the Region. Introduction of a second dose of measles vaccine in all countries was completed in January 2016 and a regional immunization verification committee has been set up. The greatest regional challenge remains low coverage with the third DTP dose, with an estimated >6 million children not fully vaccinated.

In the Region of the Americas (AMR), the outbreak of Zika virus disease is particularly demanding and the issues concerning disease surveillance were highlighted. Sustaining elimination of measles and rubella and procurement of vaccines are also of concern. The theme of the AMR World Immunization Week relates to the 2016 Olympic Games with the slogan “Go for the gold! Get vaccinated!”

SAGE stressed the critical role of NITAGs and applauded the reported progress. The importance of fostering exchanges between NITAGs was emphasized and SAGE requested a regular update on the number of established NITAGs.

Report from the GAVI Alliance

The importance of SAGE for GAVI was reiterated, noting that the upcoming Board decisions will be contingent on SAGE recommendations. These include the extension of the polio end game to 2019 which raises questions on how IPV will be supported post-2018, noting that a SAGE recommendation on IPV across different scenarios and timelines, and possible revised IPV dose schedule, will facilitate global planning.

The GAVI Programme and Policy Committee will, in May, review the WHO request for funding of RTS,S malaria vaccine pilot implementation projects.

en particulier dans les zones difficiles d'accès ou en proie à des conflits. Des progrès considérables ont été réalisés pour rétablir les services de vaccination dans le nord de la Syrie. La lutte contre l'hépatite B est en bonne voie et le processus de vérification est en cours. Les pénuries de vaccins ont suscité de vives inquiétudes, constituant un obstacle à la mise en œuvre des activités d'élimination de la rougeole. L'accent a été mis sur le problème que pose le tétanos néonatal, des orientations étant attendues de la part du SAGE pour plaider en faveur d'une allocation des ressources nécessaires à la mise en œuvre des activités associées.

La Conférence ministérielle sur la vaccination, organisée en février 2016 par les Bureaux régionaux OMS de l'Afrique et de la Méditerranée orientale en collaboration avec la Commission de l'Union africaine, a marqué un tournant historique en termes d'engagement et de promotion de la vaccination. Un suivi est assuré pour veiller à la responsabilisation et à la mise en œuvre au niveau des pays.

La Région de l'Asie du Sud-Est a rédigé un plan d'action pour les vaccins, fondé sur le Plan stratégique 2014-2017, qui sera soumis à l'approbation du groupe consultatif technique régional sur la vaccination. Des groupes consultatifs techniques nationaux sur la vaccination ont été constitués dans tous les pays de la Région. En janvier 2016, l'introduction de la seconde dose de vaccin antirougeoleux avait été menée à bonne fin dans tous les pays de la Région. Un comité régional de vérification de la vaccination a été établi. La plus grande difficulté au niveau régional demeure la faible couverture par la troisième dose de DTC: on estime à >6 millions le nombre d'enfants qui ne sont pas pleinement vaccinés.

Dans la Région des Amériques, la flambée de maladie à virus Zika est un problème particulièrement pressant et les enjeux liés à la surveillance des maladies ont été soulignés. La pérennité de l'élimination de la rougeole et de la rubéole, ainsi que l'approvisionnement en vaccins, sont également des sources de préoccupation. En référence aux Jeux olympiques de 2016, le slogan choisi pour la Semaine mondiale de la vaccination dans la Région des Amériques est «Visez l'or! Faites-vous vacciner!».

Le SAGE a souligné le rôle crucial des groupes consultatifs techniques nationaux sur la vaccination et s'est félicité des progrès accomplis à cet égard. Il a préconisé de promouvoir les échanges entre ces groupes et a demandé à être tenu régulièrement informé de leur nombre.

Rapport de l'Alliance GAVI

L'Alliance GAVI a réitéré l'importance qu'elle accorde au SAGE, indiquant que les décisions de son prochain Conseil seront tributaires des recommandations du SAGE. Parmi ces décisions figure l'extension de la phase finale d'éradication de la poliomyélite jusqu'en 2019, ce qui soulève la question des modalités d'utilisation du VPI après 2018. L'Alliance a indiqué qu'une recommandation du SAGE sur le VPI, couvrant différents scénarios et différentes échéances, avec éventuellement une révision du calendrier d'administration du VPI, faciliterait la planification au niveau mondial.

En mai, le Comité des programmes et des politiques de l'Alliance GAVI examinera la demande de l'OMS concernant le financement des projets pilotes de mise en œuvre de la vaccination antipaludique par le RTS,S.

The process for the next GAVI Vaccine Investment Strategy will start in mid-2017. Vaccines likely for re-assessment include: dengue, oral cholera, (maternal) influenza, rabies for post-exposure prophylaxis, meningococcal multivalent, hepatitis E, DTP booster, hepatitis B birth dose, typhoid conjugate and new vaccines including respiratory syncytial virus (RSV), (maternal) group B streptococcus, norovirus, and possibly others.

Global health security and GAVI's potential role in outbreak response and preparedness will be discussed by the Board, including 4 potential areas of engagement:

- 1) Stockpile investments including the extent to which GAVI should develop a more comprehensive and engaged strategy regarding vaccine stockpiles used in outbreak response;
- 2) Preparedness and response to outbreaks of diseases for which vaccines exist, which GAVI currently does not currently support, such as pandemic influenza;
- 3) Vaccines in development for emerging infectious diseases;
- 4) The extent to which GAVI should take a more deliberate approach to support countries to strengthen core capacities to prevent, detect and respond to disease outbreaks.

Programme updates include a new measles and rubella strategy, new engagement with India and a new data strategy including the need to invest more in vaccine safety.

In focusing on coverage and equity, GAVI is now implementing a country-focused strategy and bottom-up approach which includes joint appraisals and countries deciding on their technical assistance needs.

Report of the Global Advisory Committee on Vaccine Safety (GACVS)

GACVS reported on its December 2015 meeting.³ SAGE noted the continuing attention to safety concerns related to human papilloma virus (HPV) vaccines and was reassured that none of the new issues discussed in December altered the GACVS assessment of the safety of HPV vaccines. Given the substantial amount of accumulated experience and ongoing pharmacovigilance efforts that GACVS continues to stress, the main challenge regarding HPV vaccine is communicating its excellent safety profile.

SAGE was particularly interested in anxiety-related clusters, especially the body of evidence emerging on their occurrence and their potential severe impact on related

Le processus d'élaboration de la prochaine stratégie d'investissement de l'Alliance en faveur de la vaccination débutera mi-2017. Les vaccins suivants sont susceptibles de faire l'objet d'une réévaluation: vaccin contre la dengue, vaccin anticholérique oral (maternel), vaccin antigrippal, vaccin antirabique de prophylaxie post-exposition, vaccin antiméningococcique multivalent, vaccin anti-hépatite E, dose de rappel du DTC, dose à la naissance de vaccin anti-hépatite B, vaccin conjugué contre la typhoïde, ainsi que certains nouveaux vaccins, notamment contre le virus respiratoire syncytial (VRS), les infections maternelles par le streptocoque du groupe B, les norovirus, voire d'autres pathogènes.

Le Conseil abordera les questions relatives à la sécurité sanitaire mondiale et au rôle potentiel de l'Alliance GAVI dans les activités de riposte et de préparation aux flambées, ciblant notamment les 4 domaines d'engagement suivants:

- 1) investissements consacrés aux stocks de vaccins, la question étant de savoir s'il serait opportun que l'Alliance formule une stratégie plus complète et plus dynamique concernant les stocks de vaccins destinés aux activités d'intervention en cas de flambée;
- 2) préparation et riposte aux flambées de maladies contre lesquelles il existe des vaccins qui ne bénéficient pas actuellement d'un appui de l'Alliance GAVI, comme la grippe pandémique;
- 3) vaccins en cours de développement contre les maladies infectieuses émergentes;
- 4) la nécessité ou non pour l'Alliance d'adopter une approche plus délibérée pour aider les pays à renforcer les capacités essentielles requises pour prévenir, détecter et riposter aux flambées.

Au niveau programmatique, les nouveautés ont trait à la mise en place d'une nouvelle stratégie contre la rougeole et la rubéole, d'une nouvelle collaboration avec l'Inde et d'une nouvelle stratégie relative aux données, tenant compte de la nécessité d'investir davantage dans la sécurité vaccinale.

Accordant la priorité à la couverture et à l'équité, l'Alliance met désormais en œuvre une stratégie ascendante et centrée sur les pays, caractérisée par des évaluations conjointes et une approche permettant aux pays de décider de leurs propres besoins en matière d'assistance technique.

Rapport du Comité consultatif mondial de la sécurité vaccinale (GACVS)

Le GACVS a rendu compte de sa réunion de décembre 2015.³ Le SAGE a pris note de l'attention qui continue d'être portée aux inquiétudes exprimées quant à la sécurité des vaccins contre le papillomavirus humain (PVH) et s'est dit rassuré par le fait qu'aucun des points abordés en décembre n'a modifié l'évaluation faite par le GACVS de l'innocuité des vaccins. Compte tenu de l'expérience substantielle acquise à ce jour et des efforts soutenus de pharmacovigilance signalés par le GACVS, la principale difficulté, s'agissant des vaccins anti-PVH, est de mieux faire connaître leur excellent profil d'innocuité.

Le SAGE s'est particulièrement intéressé aux groupes de cas de réactions anxieuses à l'égard de la vaccination, d'autant plus qu'il existe désormais un corpus de données sur leur survenue

³ See No. 3, 2016, pp. 21–32.

³ Voir N° 3, 2016, p. 21–32.

immunization programmes. GACVS has established a working group to further develop evidence-based prevention and intervention strategies. Systematic reviews are in progress to examine anxiety clusters and their management.

SAGE commented on the safety signal detection from passive surveillance data as conducted by the Uppsala Monitoring Centre (UMC). SAGE was concerned that these signals are not undergoing appropriate peer review and concurred with GACVS on the need to increase collaboration in a strong review process. Since most of the vaccine-related data in the UMC database come from a smaller group of high income countries, SAGE urged that efforts be pursued to enhance AEFI reporting worldwide.

Respiratory syncytial virus vaccine development pipeline

A systematic literature review estimated that 33.8 (95% CI 19.3–46.2) million episodes of respiratory syncytial virus (RSV) associated acute lower respiratory infections (ALRI) occur annually in children aged <5 years (22% of ALRI episodes), with approximately 3.4 (2.8–4.3) million episodes representing severe RSV-associated ALRI necessitating hospital admission. An estimated 66 000–199 000 children aged <5 years died from RSV-associated ALRI in 2005, with 99% of these deaths occurring in developing countries.

The RSV vaccine and immunization pipeline consists of 3 main classes of products: subunit vaccines mainly in development for maternal immunization; live attenuated or recombinant viral vaccines for active paediatric vaccination; and long-acting monoclonal antibodies (mAb) targeted for seasonal or birth dosing using a one-dose regimen. There are >60 candidate vaccines, mostly in pre-clinical development and 16 currently in clinical trials. Of these, one recombinant protein approach is undergoing clinical trial Phase 3 evaluation in pregnant women, and one long-acting mAb is in Phase 2 testing. Of note, there is an existing licensed mAb (requiring repeat dosing), raising the chances of success for the next generation of long-acting mAb approaches.

In March 2015, WHO convened a meeting of scientists, public health officials and regulators from low, middle and high income countries, at which the need to clarify pathways towards policy recommendations, prequalification and financing of RSV vaccines and long-acting mAbs was stressed.

RSV surveillance is being added as a pilot component to the WHO Global Influenza Surveillance and Response System which is fully functional in 110 countries. The key policy questions for understanding RSV disease burden will need to be embedded into the surveillance

et leurs conséquences potentielles graves sur les programmes de vaccination correspondants. Le GACVS a créé un groupe de travail chargé de poursuivre les efforts de développement de stratégies de prévention et d'intervention sur la base de données probantes. Des analyses systématiques sont en cours, consistant à examiner les groupes de cas de réactions anxieuses signalés et à étudier la manière dont ils ont été abordés.

S'agissant de la détection des signaux de sécurité à partir des données de surveillance passive au centre collaborateur d'Uppsala, le SAGE s'est dit préoccupé par le fait que ces signaux ne font l'objet d'aucun examen approprié par les pairs et a souscrit à la position du GACVS quant à la nécessité d'une collaboration accrue dans le cadre d'un processus d'examen rigoureux. Puisque la plupart des données liées aux vaccins contenues dans la base de données du centre d'Uppsala proviennent d'un petit groupe de pays à revenu élevé, le SAGE a vivement recommandé de poursuivre les efforts visant à améliorer la notification des manifestations postvaccinales indésirables à l'échelle mondiale.

Vaccins en préparation contre le virus respiratoire syncytial

Selon une analyse systématique de la littérature, on estime que 33,8 millions (IC à 95%: 19,3 46,2 millions) d'épisodes d'infection aiguë des voies respiratoires inférieures (IARI) dus au virus respiratoire syncytial (VRS) surviennent chaque année chez les enfants de <5 ans (22% de tous les épisodes d'IARI), dont environ 3,4 millions (2,8-4,3) sont des cas graves d'IARI dus au VRS, exigeant une hospitalisation. Quelque 66 000 à 199 000 enfants de <5 ans sont décédés d'une infection aiguë des voies respiratoires inférieures en 2005, 99% d'entre eux dans des pays en développement.

Les produits d'immunisation anti-VRS en cours de développement sont de 3 types: vaccins sous-unités, mis au point principalement aux fins de l'immunisation maternelle; vaccins viraux recombinants ou vivants atténués destinés à la vaccination de l'enfant; et anticorps monoclonaux à action prolongée dont la posologie consistera en l'administration saisonnière ou à la naissance d'une dose unique. Il existe >60 vaccins candidats; la plupart sont en phase de développement préclinique et 16 font actuellement l'objet d'essais cliniques. Parmi ces derniers, un vaccin à protéine recombinante est en cours d'évaluation clinique de phase 3 chez la femme enceinte et un anticorps monoclonal à action prolongée fait l'objet d'une évaluation de phase 2. Il convient de noter qu'il existe déjà un anticorps monoclonal homologué (devant être administré par doses répétées), ce qui est de bon augure pour la prochaine génération d'anticorps monoclonaux à action prolongée.

En mars 2015, l'OMS a organisé une réunion de scientifiques, de responsables de la santé publique et de représentants d'organismes de réglementation provenant de pays à revenu faible, intermédiaire et élevé. Les participants ont souligné qu'il était nécessaire de clarifier les procédures requises pour parvenir à des recommandations politiques, à la préqualification et au financement des vaccins anti-VRS et des anticorps monoclonaux à action prolongée.

La surveillance du VRS a été intégrée, en tant que composante pilote, au Système mondial de surveillance de la grippe et de riposte de l'OMS, actuellement pleinement opérationnel dans 110 pays. Les principales questions politiques relatives à la charge de morbidité du VRS devront être incorporées au travail

work in addition to characterization of seasonality and strain selection. SAGE noted the importance of including sentinel surveillance sites that will provide incidence estimates including denominators.

In terms of international standard reagents, the initial priority is for neutralization assays which are considered the primary serological endpoint for RSV vaccines. A work plan and timeline for development of RSV international standard reagents will be presented to the Expert Committee on Biological Standardization in 2016.

SAGE identified key gaps in age-stratified disease burden data, whether protection against subsequent severe infections following a primary infection exists, community mortality data, morbidity and mortality among pregnant women and the elderly, economic consequences and additional burden from Africa and South Asia.

SAGE suggested mobilizing resources to follow up subjects from randomized controlled trials to evaluate the long term effects of RSV interventions in the context of uncertainties on whether RSV infection causes recurrent wheeze, which, if demonstrated, would substantially increase the cost-effectiveness of RSV preventive interventions.

SAGE asked for preparations to be made to support global policy-making for RSV maternal immunization as well as passive immunization with long-acting mAb. SAGE emphasized the need to link maternal immunization platform strengthening with influenza, tetanus and pertussis vaccines along with preparations for potential country introductions of RSV vaccine. This will require close coordination between immunization implementation, respiratory infection, reproductive health, child health researchers and vaccine safety communities. SAGE encouraged determination of prequalification pathways for long-acting mAb and initiation of early discussions with financing bodies to achieve potential major public health value of RSV vaccination that may become available in the next 5 years.

SAGE confirmed that the generation of cost-effectiveness and impact data was a priority for RSV immunization. The displacement implications of the large surge in RSV hospitalizations during annual seasonal peaks should also be factored into the health economic work.

SAGE recommended that the current critical 4–5 year interval should be used to systematically identify and fill gaps in evidence required from regulatory, prequalification and policy recommendation perspectives for RSV preventive interventions, including maternal immunization, passive immunization with long-acting mAb and paediatric immunization.

de surveillance, en sus de la caractérisation de la saisonnalité et de la sélection des souches. Le SAGE a indiqué qu'il est important d'inclure des sites de surveillance sentinelle qui fourniront des estimations de l'incidence, notamment les valeurs utilisées en dénominateur.

Pour ce qui est des réactifs de référence internationaux, la priorité sera initialement accordée aux épreuves de neutralisation, considérées comme le critère de jugement sérologique primaire pour les vaccins anti-VRS. Un plan de travail et un calendrier de développement des réactifs de référence internationaux seront présentés au Comité d'experts de la standardisation biologique en 2016.

Le SAGE a identifié des lacunes importantes dans les données existantes sur la charge de morbidité selon l'âge, sur la protection conférée par une première infection contre les infections graves ultérieures, sur la mortalité au niveau communautaire, sur la morbidité et la mortalité chez les femmes enceintes et les personnes âgées, sur les incidences économiques de la maladie et sur ses autres conséquences en Afrique et en Asie du Sud.

Le SAGE a suggéré de mobiliser les ressources nécessaires au suivi des sujets ayant participé à des essais contrôlés randomisés afin d'évaluer les effets à long terme des interventions anti-VRS. On soupçonne que l'infection par le VRS pourrait provoquer des sifflements respiratoires récurrents, une hypothèse qui, si elle est confirmée, augmenterait considérablement le rapport coût/efficacité des interventions de prévention contre le VRS.

Le SAGE a demandé que des préparatifs soient engagés pour appuyer l'élaboration des politiques mondiales sur la vaccination maternelle contre le VRS, ainsi que sur l'immunisation passive par les anticorps monoclonaux à action prolongée. Le SAGE a souligné la nécessité d'associer le renforcement du programme de vaccination maternelle contre la grippe, le tétanos et la coqueluche aux activités de préparation à l'introduction potentielle du vaccin anti-VRS dans le pays. Cela suppose une étroite coordination entre les responsables de la mise en œuvre de la vaccination, les chercheurs dans les domaines des infections respiratoires, de la santé reproductive et de la santé de l'enfant, et les acteurs de la sécurité vaccinale. Le SAGE a conseillé de définir les voies de préqualification des anticorps monoclonaux à action prolongée et d'engager des discussions préliminaires avec les organismes de financement pour permettre aux vaccins anti-VRS susceptibles d'entrer sur le marché au cours des 5 prochaines années d'être porteurs d'une valeur potentielle considérable en termes de santé publique.

Le SAGE a confirmé que la production de données sur le rapport coût/efficacité et l'impact des produits d'immunisation anti-VRS constitue une priorité. L'incidence des déplacements liés à la forte augmentation des hospitalisations dues au VRS lors des pics saisonniers annuels doit également être prise en compte dans les évaluations économiques sanitaires.

Le SAGE a recommandé d'utiliser la période critique actuelle de 4-5 ans pour identifier et combler de manière systématique les lacunes existant au niveau des données requises aux fins de l'approbation réglementaire, de la préqualification et de la formulation de recommandations politiques pour les interventions de prévention contre le VRS, y compris la vaccination maternelle, l'immunisation passive par des anticorps monoclonaux à action prolongée et la vaccination pédiatrique.

SAGE also recommended that WHO endorse the importance and ethical imperative of clinical trials in pregnant women for potentially life-saving interventions such as RSV vaccine (and future vaccines against other targets currently in development, such as group B streptococcal disease).

Polio eradication

In October 2015, SAGE reaffirmed that withdrawal of type 2 oral polio vaccine (OPV2) should proceed in April 2016 through a globally synchronised switch from trivalent to bivalent OPV (tOPV-bOPV switch). At that meeting, SAGE recognized that a significant shortfall in IPV supply meant that some countries would not be able to introduce IPV into their routine immunization schedules until well after the switch. Despite this constraint, SAGE confirmed that the switch should proceed, even in the event of further shortfalls because IPV will be primarily a risk mitigation tool to reduce the risk of paralysis if a type 2 vaccine-derived poliovirus (VDPV2) emerges post-switch. However, use of IPV does not reduce the risk of VDPV emergence. Furthermore, should a VDPV2 emerge post-switch, sufficient stockpiles of monovalent OPV2 (mOPV2) and IPV are available at the global level to be distributed to countries in need, on approval by the Director-General of WHO. SAGE concluded that the public health risks associated with the continued use of the type 2-containing vaccine outweigh the risks associated with proceeding with the switch despite an IPV shortage.

Global IPV supply further declined in March 2016, due to challenges in rapid scale-up of production. SAGE issued a statement in March 2016 re-affirming that countries should stop using tOPV in April 2016 regardless of the timing of IPV introduction or national disruptions in IPV supply. To promote dose-sparing, SAGE encouraged countries to evaluate the cost-benefits, trade-offs and programmatic feasibility associated with providing IPV in a 2-dose fractional intra-dermal dose schedule, e.g. at 6 and 14 weeks, in lieu of a single intramuscular dose at 14 weeks.

SAGE reviewed the overall progress of the Global Polio Eradication Initiative (GPEI) and the implementation of OPV2 withdrawal, and had initial discussions on future polio immunization policy. SAGE acknowledged the significant progress made towards eliminating wild poliovirus (WPV) in Afghanistan and Pakistan with improved access, coordination and operations. Lower performing areas in both countries are well-defined and specific plans are being implemented to take advantage of the low transmission season. SAGE noted the importance of the environmental sampling efforts in these countries to inform and support continued efforts of the programme. There has been progress in eliminating persistent VDPV2 in Pakistan and Nigeria with no case since May 2015. Over the last 6 months there have been VDPV2 outbreaks in Myanmar and Guinea and one VDPV2 case in the Democratic Republic of Congo

Le SAGE a également invité l'OMS à affirmer l'importance et l'impératif éthique des essais cliniques chez la femme enceinte pour les interventions susceptibles de sauver des vies, comme la vaccination anti-VRS (et les futurs vaccins actuellement en développement contre d'autres cibles, notamment contre la maladie à streptocoques du groupe B).

Éradication de la poliomyélite

En octobre 2015, le SAGE avait réaffirmé que le retrait du vaccin antipoliomyélitique oral de type 2 (VPO2) aurait lieu en avril 2016 au moyen d'une transition synchronisée à l'échelle mondiale du VPO trivalent (VPOt) au VPO bivalent (VPOb). Lors de cette réunion, le SAGE avait reconnu qu'en raison d'une pénurie significative de vaccin antipoliomyélitique inactivé (VPI), certains pays ne seraient en mesure d'introduire le VPI dans leur calendrier de vaccination systématique que bien après la transition. Malgré cette difficulté, le SAGE a confirmé que la transition doit avoir lieu comme prévu, même en cas d'aggravation de la pénurie, car le VPI servira essentiellement à réduire les risques de paralysie en cas d'émergence de poliovirus dérivé d'une souche vaccinale de type 2 (PVDV2) après la transition. Cependant, l'utilisation du VPI ne réduit pas le risque d'émergence de PVDV. En outre, dans l'hypothèse d'une émergence de PVDV2 après la transition, des réserves suffisantes de VPO2 monovalent (VPOm2) et de VPI sont disponibles à l'échelle mondiale pour pouvoir être distribuées aux pays qui en auraient besoin, sur approbation du Directeur général de l'OMS. Le SAGE a conclu que les risques de santé publique associés à l'utilisation persistante du vaccin contenant la composante de type 2 l'emportent sur les risques de la transition, en dépit de la pénurie de VPI.

En mars 2016, l'approvisionnement mondial en VPI a accusé un nouveau déclin en raison de difficultés liées à l'augmentation massive et rapide de la production. Le SAGE a publié une déclaration en mars 2016, dans laquelle il réaffirmait que les pays devront cesser d'utiliser le VPOt en avril 2016, indépendamment de la date d'introduction du VPI et des difficultés d'approvisionnement en VPI rencontrées par les pays. Pour favoriser les économies de doses, le SAGE a encouragé les pays à évaluer le rapport coûts/avantages, la faisabilité programmatique et les compromis qu'impliquerait l'administration du VPI selon un schéma à 2 doses fractionnées intradermiques, à 6 semaines et 14 semaines, au lieu d'une dose intramusculaire unique à 14 semaines.

Le SAGE a examiné les progrès accomplis par l'Initiative mondiale pour l'éradication de la poliomyélite (IMEP) et la mise en œuvre du retrait du VPO2 et a engagé des discussions sur les politiques futures de vaccination antipoliomyélitique. Le SAGE a salué les progrès considérables réalisés en vue d'éliminer le poliovirus sauvage (PVS) en Afghanistan et au Pakistan, grâce à une amélioration de l'accès, de la coordination et des opérations. Au sein de ces 2 pays, les zones enregistrant des résultats moins satisfaisants sont bien définies et des plans spécifiques sont actuellement mis en œuvre pour profiter de la saison de faible transmission. Le SAGE a souligné l'importance des prélèvements d'échantillons environnementaux dans ces pays afin de guider et d'appuyer les futures activités du programme. Les efforts d'élimination du PVDV2 persistant au Pakistan et au Nigéria ont progressé, aucun cas n'ayant été signalé depuis mai 2015. Au cours des 6 derniers mois, on a observé des flambées de PVDV2 au Myanmar et en Guinée, ainsi

(DRC). SAGE concluded that the response to the VDPV2 outbreak in Myanmar is adequate. However, there was concern about the situations in Guinea and DRC with evidence of inadequate surveillance. SAGE recommended that GPEI should ensure high quality supplementary immunization activities (SIAs) in Guinea and DRC, if necessary with mOPV2 after April 2016, and to intensify programme surveillance in these countries, and in Sierra Leone and Liberia as they recover from the Ebola epidemic.

SAGE noted the strong and sustained progress towards addressing the readiness criteria for the OPV2 withdrawal. To date, 94/126 OPV countries have introduced IPV into their routine immunization. However, SAGE reiterated its concern over the global IPV supply shortage, which will likely persist into 2017/18. SAGE urged that IPV suppliers make best efforts to fulfil their commitment to supply IPV, accommodate the needs of the programme (e.g. supplying more vaccine in 1-dose or 5-dose vials to reduce wastage), and inform the SAGE Polio Working Group of any further change in the IPV supply situation. SAGE requested that WHO address concerns of countries affected by the IPV supply situation via frequent and clear communications and providing technical support. It also requested the Working Group to evaluate options for catch-up vaccination for cohorts born after 1 May 2016 in countries where IPV introduction will be delayed or regular supply disrupted.

SAGE noted that a small number (≤ 2) of cVDPV2 outbreaks are expected within 12 months after the switch. It recommended that GPEI enhance surveillance in countries with high risk of VDPV emergence and in countries without IPV, and respond to any VDPV2 emergence as an emergency, as per the updated response protocol. WHO should also amend the surveillance case definition to include type 2 Sabin so that all type 2 polioviruses will be notifiable under the IHR.

SAGE acknowledged the progress made in completing the containment phase I (i.e. reducing the number of facilities containing poliovirus) for WPV2/VPDV2 in most countries, under the Global Action Plan for Containment (GAP III). SAGE urges all countries to ensure completion of phase I for all type 2 poliovirus, including Sabin 2, and to strengthen national intersectoral collaboration to comply with phase II of GAPIII (i.e. reduce risk in facilities containing poliovirus).

Lastly, SAGE reviewed the Polio Working Group discussion on future polio immunization policy. The Working Group proposed to work on the following recommendations: (i) an explicit decision on whether polio vaccination should be continued after global certification of eradication; (ii) the recommended IPV schedule (number of doses, timing, formulation) after OPV withdrawal; and (iii) the criteria for when countries could stop polio vaccination (e.g. surveillance capacity,

qu'un cas de PVDV2 en République démocratique du Congo (RDC). Le SAGE a estimé que la riposte menée contre la flambée de PVDV2 au Myanmar est satisfaisante. Il a en revanche exprimé des inquiétudes quant à la situation en Guinée et en RDC, les données indiquant une insuffisance de la surveillance. Le SAGE a recommandé que l'IMEP veille à l'organisation d'activités de vaccination supplémentaire (AVS) de qualité en Guinée et en RDC, si nécessaire avec le VPOM2 après avril 2016, et à l'intensification de la surveillance dans ces pays, ainsi qu'en Sierra Leone et au Libéria, pays en phase de relèvement suite à l'épidémie d'Ebola.

Le SAGE a observé les progrès importants et durables réalisés pour que les critères de préparation au retrait du VPO2 soient satisfaits. À ce jour, 94 des 126 pays utilisant le VPO ont introduit le VPI dans leur programme de vaccination systématique. Toutefois, le SAGE a de nouveau exprimé son inquiétude face à la pénurie mondiale de VPI, qui durera probablement jusqu'en 2017-2018. Le SAGE a appelé les fournisseurs de VPI à faire tout leur possible pour tenir leurs engagements d'approvisionnement, répondre aux besoins du programme (par exemple en fournissant davantage de vaccins en flacons de 1 dose ou 5 doses pour réduire le gaspillage), et informer le Groupe de travail sur la poliomyélite du SAGE de toute nouvelle évolution de l'approvisionnement en VPI. Le SAGE a demandé à l'OMS de répondre aux préoccupations exprimées par les pays concernés par les difficultés d'approvisionnement en VPI en assurant une communication claire et régulière et en offrant un appui technique. Il a également demandé au Groupe de travail d'évaluer les options de vaccination de rattrapage pour les cohortes nées après le 1er mai 2016 dans les pays confrontés à une introduction retardée du VPI ou à une perturbation de l'approvisionnement habituel.

Le SAGE a indiqué qu'un nombre très limité (≤ 2) de flambées de PVDVc2 peut être escompté dans les 12 mois suivant la transition. Il a recommandé à l'IMEP de renforcer la surveillance dans les pays exposés à un risque élevé d'émergence de PVDV et dans les pays sans VPI, et de traiter toute émergence de PVDV2 comme une urgence, conformément au protocole de riposte actualisé. Il convient également que l'OMS modifie la définition de cas utilisée pour la surveillance afin d'inclure la souche Sabin de type 2, tous les poliovirus de type 2 devant dès lors obligatoirement être notifiés au titre du RSI.

Le SAGE a salué les progrès accomplis dans la plupart des pays pour achever la Phase I de confinement du PVS2/PVDV2 (réduction du nombre d'établissements détenant le poliovirus) en vertu du Plan d'action mondial pour le confinement (GAPIII). Le SAGE invite instamment tous les pays à achever la Phase I pour tous les poliovirus de type 2, y compris la souche Sabin 2, et à renforcer la collaboration intersectorielle nationale en vue de remplir les critères de la Phase II du GAPIII (réduction du risque dans les établissements détenant le poliovirus).

Enfin, le SAGE a passé en revue les discussions menées par le Groupe de travail sur la poliomyélite au sujet des futures politiques de vaccination antipoliomyélitique. Le Groupe de travail a proposé d'œuvrer à l'élaboration des recommandations suivantes: i) une décision explicite sur la pertinence d'une poursuite de la vaccination antipoliomyélitique après la certification mondiale de l'éradication; ii) le schéma recommandé d'administration du VPI (nombre de doses, calendrier, formulation) après le retrait du VPO; et iii) les critères déterminant quand

absence of immunodeficiency-related vaccine-derived poliovirus [iVDPV]), based on vaccine and funding availability and expected vaccine price. SAGE agreed with the proposed approach and requested the Working Group to present a high-level policy direction in October 2016 and finalize its recommendations on future immunization policies for consideration by SAGE in October 2017.

Implementation of immunization in the context of Health Systems Strengthening and Universal Health Coverage

The session addressed the request from SAGE to give attention to HSS, and explore how it can contribute towards ensuring equitable and sustainable immunization goals in countries as per the GVAP, and in line with the SDGs and Universal Health Coverage (UHC).

The session was organized around 2 presentations, the first providing an overview of current and future dimensions of HSS in supporting UHC and SDGs, and the second providing perspective on implementation, issues and challenges in integrating immunization services into national and subnational health systems. The presentations highlighted the compatibility of the SDGs with the need for a health systems approach to attain sustainable health outcomes, including for immunization. A radical departure from current programme designs is needed to take cognizance of changes in service delivery expectations. A classification of health system focus for fragile least developed (tier 1), other less developed (tier 2) and mature (tier 3) countries was proposed. Resilience of the system would be a critical element as well as sufficient well-balanced investments in the health system.

A systems perspective remains the best way for immunization programmes to take forward their goals in a sustainable manner. The need to include a clear aspirational indicator for immunization within the SDG monitoring was discussed. The following conclusions were agreed:

- Many new vaccines require special service delivery approaches due to their nature. HSS initiatives need to recognize such situations, which are becoming more common.
- Emergencies and crises are becoming common and complex in many countries. This requires a more indepth understanding of resilience of systems at national and subnational levels to ensure countries are able to absorb disruptions, or adapt/respond to changing needs on a continuous basis.
- It is important to recognize the role of national leadership and capacity building, and the use of data/implementation research to create policy

les pays peuvent arrêter la vaccination antipoliomyélitique (par exemple, capacités de la surveillance, absence de poliovirus dérivé d'une souche vaccinale associé à une immunodéficience [PVDVi]), selon la disponibilité des vaccins et des fonds nécessaires, ainsi que le prix escompté du vaccin. Le SAGE a souscrit à la démarche proposée. Il a demandé au Groupe de travail de présenter des orientations politiques générales en octobre 2016, puis de formuler des recommandations définitives sur les futures politiques de vaccination, à soumettre à l'examen du SAGE en octobre 2017.

Mise en œuvre de la vaccination dans le contexte du renforcement des systèmes de santé et de la couverture sanitaire universelle

Cette séance a été organisée pour répondre au souhait du SAGE de s'intéresser au renforcement des systèmes de santé et de déterminer dans quelle mesure il peut contribuer à la réalisation des objectifs de vaccination équitable et durable dans les pays, conformément au Plan d'action mondial pour les vaccins et en harmonie avec les ODD et la couverture sanitaire universelle.

La séance s'est articulée autour de 2 présentations, la première décrivant les dimensions actuelles et futures du renforcement des systèmes de santé à l'appui de la couverture sanitaire universelle et des ODD, et la seconde offrant une perspective sur la mise en œuvre, les problèmes et les enjeux de l'intégration des services de vaccination dans les systèmes de santé nationaux et infranationaux. Ces présentations ont clairement montré que les ODD sont compatibles avec la nécessité d'une démarche fondée sur les systèmes de santé pour atteindre des résultats sanitaires durables, y compris en matière de vaccination. Un changement radical des méthodologies programmatiques actuelles sera nécessaire pour discerner l'évolution des attentes en matière de prestation de services. Une classification des priorités pour les systèmes de santé a été proposée, selon que le pays appartient au groupe des pays fragiles les moins avancés (niveau 1), des autres pays moins avancés (niveau 2) ou des pays avancés (niveau 3). La résilience du système constitue un élément essentiel, tout comme la présence d'investissements suffisants et équilibrés dans le système de santé.

Une approche fondée sur les systèmes demeure le meilleur moyen pour les programmes de vaccination de parvenir à leurs objectifs de manière durable. La discussion a également porté sur la nécessité d'inclure un indicateur de vaccination idéal clairement défini dans le cadre du suivi des ODD. Le SAGE est parvenu aux conclusions suivantes:

- De par leur nature, de nombreux nouveaux vaccins exigent des modalités de prestation de services particulières. Les initiatives de renforcement des systèmes de santé doivent tenir compte des situations de ce type, qui sont de plus en plus courantes.
- De nombreux pays connaissent des situations d'urgence et de crise, devenues plus fréquentes et plus complexes. Il est donc essentiel d'avoir une connaissance approfondie de la résilience des systèmes aux niveaux national et infranational pour apprécier la capacité des pays à résister aux perturbations et à s'adapter en permanence à l'évolution des besoins.
- Il est important de reconnaître le rôle des activités de direction et de renforcement des capacités au niveau national, ainsi que l'utilisation des données/de la recherche sur la

dialogue at the national level. Good governance and decision-making has to come from policy dialogue based on evidence-base/science at national levels.

- There is a recognized need for immunization services to better align with the other HSS initiatives, to ensure sustainable and adequate outcomes.
- The word 'research' can, in some contexts, be misunderstood as research is perceived as being outside service delivery, and may not be recognized as an important part of HSS. Regardless of the terms used, the focus needs to be on generation of evidence and use of the evidence for policy and action. There are good best practice models and case studies – much could be learnt from sharing these, particularly for tier 1 and 2 countries.
- There is a need to define indicators that will allow better HSS monitoring.

Potential areas for implementation research are wide and cross-cutting issues should be considered, such as assessment of efficiency and effectiveness of delivery systems and required financial investments. There are considerable gaps in the research agenda in the areas of surveillance, health systems, governance, integrated service delivery, health products, costs and financing, equity, and partnership with communities.

It is critical to ensure that services are people-centred and not limited to products. Beyond a focus on improving access to immunization services, a focus is also needed on improving the quality of all the care the person needs, and ensuring real demand by populations to attain desired outcomes from investments. Flexibility is needed to ensure optimized service delivery at national and subnational levels. SAGE noted the advancements in knowledge in the field of HSS, which should support the attainment of immunization goals in a sustainable manner. The need to embed health systems thinking in every initiative and action, without losing goals so far attained, was appreciated by SAGE as a way forward. SAGE emphasized the importance of ensuring the visibility of immunization goals in planning HSS efforts. A system to generate data for evidence-based decision-making, with a focus on implementation research, is a route to achieving this. It was proposed that implementation research take up specific challenges that lead to strengthening of health systems. Improvement of immunization services within the broader health services should be a third dimension of vaccine programmes alongside safety and effectiveness, and this will need appropriate long term funding. SAGE recommended that WHO promote further progress in this arena more actively, and that a preparatory team continue the dialogue and develop a more targeted agenda.

mise en œuvre pour établir un dialogue politique national. La bonne gouvernance et le processus de décision doivent reposer sur un dialogue politique fondé sur des données scientifiques probantes au niveau national.

- Il est reconnu qu'un meilleur alignement entre les services de vaccination et les autres initiatives de renforcement des systèmes de santé est nécessaire pour parvenir à des résultats satisfaisants et durables.
- Le terme «recherche» peut être mal compris dans certains contextes, la recherche étant perçue comme une activité externe à la prestation de services et risquant donc de ne pas être reconnue comme une composante importante du renforcement des systèmes de santé. Quelle que soit la terminologie utilisée, l'accent doit être mis sur la génération de données probantes utilisées pour orienter les décisions politiques et l'action. Il existe des modèles de meilleures pratiques et des études de cas de bonne qualité, à partir desquels des enseignements précieux pourraient être tirés, en particulier dans les pays des niveaux 1 et 2.
- Il est nécessaire de définir des indicateurs permettant un meilleur suivi du renforcement des systèmes de santé.

Les domaines de recherche potentiels sur la mise en œuvre étant vastes, il convient de tenir compte des questions transversales, comme l'évaluation de l'efficacité et de l'efficacités des systèmes de prestation et les investissements financiers requis. Le programme de recherche comporte des lacunes substantielles dans les domaines de la surveillance, des systèmes de santé, de la gouvernance, de la prestation de services intégrés, des produits sanitaires, des coûts et du financement, de l'équité et de l'établissement de partenariats avec les communautés.

Il est indispensable que les services soient centrés sur la personne et ne se limitent pas aux produits. Au-delà de l'objectif visant à accroître l'accès aux services de vaccination, l'accent doit également être mis sur l'amélioration de la qualité de tous les soins dont la personne a besoin, ainsi que sur la demande réelle de la population, pour que les investissements consentis donnent les résultats souhaités. Une certaine souplesse est nécessaire pour optimiser la prestation de services aux niveaux national et infranational. Le SAGE a constaté que les connaissances en matière de renforcement des systèmes de santé ont progressé, ce qui devrait permettre d'atteindre durablement les objectifs de vaccination. Le SAGE a estimé que la voie à suivre consiste à intégrer une réflexion sur les systèmes de santé dans toute initiative ou action entreprise, sans régresser sur les objectifs déjà atteints. Le SAGE a souligné qu'il importe de veiller à la visibilité des objectifs de vaccination lors de la planification des efforts de renforcement des systèmes de santé. L'utilisation d'un système générant des données pouvant orienter la prise de décisions sur des bases factuelles, axé en particulier sur la recherche sur la mise en œuvre, est un moyen de parvenir à cette fin. Il a été proposé de faire porter la recherche relative à la mise en œuvre sur des enjeux spécifiques qui pourront mener au renforcement des systèmes de santé. L'amélioration des services de vaccination, dans le cadre plus large des services de santé, doit être le troisième volet des programmes de vaccination, les 2 premiers étant la sécurité et l'efficacité; cet effort exige un financement adéquat à long terme. Le SAGE a recommandé que l'OMS s'emploie plus activement à favoriser les progrès dans ce domaine et qu'une équipe préparatoire assure la poursuite du dialogue engagé et élabore un programme plus ciblé.

Pre-empting and responding to vaccine supply shortages

Over the past 2 years, various countries across regions and income groups have reported shortages of vaccines, sometimes causing critical disruptions of services. This has been reported for multiple vaccines, including yellow fever, BCG, DTP, acellular pertussis containing vaccines and IPV. Various essential medicines have also been in short supply in recent years. Countries have expressed their concerns to WHO and are requesting more information and solutions in order to mitigate the effects of current vaccine and drug shortages and prevent them in future.

Access to timely and affordable supplies of vaccines is an integrated component of the Middle Income Countries (MIC) strategy, presented at SAGE in April 2015, and of Resolution 68.6 on the GVAP, adopted in May 2015 by the World Health Assembly (WHA). A resolution is currently being prepared for consideration at this year's WHA on "Addressing the global shortages of medicines".

Presentations highlighted the reasons behind the vaccine shortages, the impact in countries, collaboration and communication done by regional bodies and international collaboration of partners supporting global activities and long term strategic supply security. Reasons behind shortages are multiple and vary for different vaccines and markets. Several partners are active on these causes at global level, but most have a restrictive focus area, leaving some countries more at risk of shortages, notably self-procuring countries and particularly the self-procuring MICs. Moreover, the lack of a global mechanism to capture information or provide guidance for all countries and all products limits the possibility to identify, assess and manage shortages.

The session generated extensive discussion; following are the main points:

1. Information collection and sharing was recognized as a major area for potential further investment. The role of WHO was discussed particularly in relation to self-procuring countries not currently benefitting from international efforts in this area. SAGE recognized clear links between this discussion and the draft resolution to be submitted to the WHA in May.
2. The importance of taking into account and acting upon the multiple causes and dimension of shortages was emphasized. While pricing of vaccines is one factor, SAGE discussed the importance of various other issues including strengthening country decision-making processes in the context of supply restrictions, demand forecasting capabilities, the use of effective vaccine management as a tool to increase efficiency of supply, and the need to adapt in-country procurement practices (through the

Prévention et intervention face aux pénuries de vaccins

Au cours des 2 dernières années, plusieurs pays, appartenant à différentes régions et différentes catégories de revenu, ont signalé des pénuries de vaccins, entraînant parfois une perturbation critique des services. Cette situation concerne plusieurs vaccins, dont le vaccin anti-amaril, le BCG, le DTC, les vaccins antioquelucheux acellulaires et le VPI. Divers médicaments essentiels sont également venus à manquer ces dernières années. Les pays ont fait part de leurs préoccupations à l'OMS, demandant à l'Organisation de fournir des informations complémentaires, ainsi que des solutions permettant d'atténuer les effets des pénuries actuelles de vaccins et de médicaments et de les prévenir à l'avenir.

L'accès aux vaccins en temps utile et à un prix abordable est une partie intégrante de la stratégie pour les pays à revenu intermédiaire, présentée à la réunion du SAGE d'avril 2015, ainsi que de la résolution WHA68.6 sur le Plan d'action mondial pour les vaccins, adoptée par l'Assemblée mondiale de la Santé en mai 2015. Une résolution intitulée «Lutter contre les pénuries mondiales de médicaments» est en cours d'élaboration, devant être soumise à l'Assemblée mondiale de la Santé cette année.

Les informations présentées au SAGE portaient sur les causes des pénuries de vaccins, leur incidence sur les pays, les efforts de collaboration et de communication déployés par les organismes régionaux et la collaboration internationale entre les acteurs intervenant dans les activités mondiales et œuvrant à la sécurité à long terme des approvisionnements stratégiques. Les causes de ces pénuries sont nombreuses et diffèrent selon les vaccins et les marchés. Plusieurs partenaires s'emploient à remédier à ces causes au niveau mondial, mais la plupart d'entre eux ont un domaine d'action limité, laissant certains pays plus exposés aux pénuries, en particulier les pays qui se procurent les vaccins eux-mêmes, surtout lorsqu'il s'agit de pays à revenu intermédiaire. En outre, l'absence d'un mécanisme mondial destiné à enregistrer les informations et à fournir des orientations à tous les pays sur tous les produits limite les possibilités d'identification, d'évaluation et de gestion des pénuries.

Cette séance a suscité de longs débats, s'articulant autour des principaux points suivants:

1. Il a été souligné que la collecte et l'échange des informations constituent un domaine important d'investissement potentiel pour l'avenir. Les discussions ont porté sur le rôle de l'OMS, en particulier à l'égard des pays qui se procurent eux-mêmes les vaccins et qui ne bénéficient pas actuellement des efforts internationaux consentis dans ce domaine. Le SAGE a constaté la relation manifeste existant entre ce débat et le projet de résolution devant être soumis à l'Assemblée mondiale de la Santé en mai.
2. Le SAGE a souligné qu'il importe de tenir compte des causes et dimensions multiples de ces pénuries et d'agir en conséquence. Outre le prix des vaccins, le SAGE a discuté de l'importance de divers autres facteurs, notamment le renforcement du processus décisionnel des pays dans un contexte de restrictions de l'approvisionnement, les capacités de prévision de la demande, la mise en œuvre d'une bonne gestion des vaccins pour accroître l'efficacité de l'approvisionnement, et la nécessité d'adapter les pratiques d'approvisionnement des pays (en passant d'une démarche transac-

- transition from transactional procurement to strategic supply management; exploring benefits of pool procurement activities).
3. The need to rationalize product and regulatory requirements was particularly stressed. It was suggested that regulators should meet to discuss how regulatory processes can become more coherent and flexible. Supranational regulatory agencies may have a role to play in advising and providing scientific advice to national regulatory agencies on unregistered products.
 4. It was noted that in addition to new activities, long term strategies targeting vaccine supply security are important and should be continued.

SAGE recommended that WHO could play a key role in setting up an “Exchange Forum”, helping to collect demand information from all Member States and to enhance dialogue between countries’ demand (including anticipation of schedule evolution and new introductions) and manufacturers’ supply availability and risks. SAGE recognized that WHO would be able to take on this role if financial resources were made available and if all key partners (such as UNICEF Supply Division, the Bill & Melinda Gates Foundation, GAVI, vaccine manufacturers and countries) would engage and commit to this activity.

SAGE proposed as immediate action to communicate effectively to countries on causes of shortages and current mitigation and long term activities. This would provide a necessary level of confidence in countries that the topic is not being overlooked, given the recognized impact of shortages on community level trust in immunization programmes.

Missed opportunities for vaccination

Concerned about stagnating immunization coverage, during its 2014 review of the GVAP SAGE recommended studies to understand how opportunities to vaccinate are being missed by health-care workers and their tracking systems, and action to markedly reduce their incidence.⁴ SAGE was informed on the status of this area of work and requested to endorse the components of the updated strategy to reduce missed opportunities for vaccination (MOV).

A MOV occurs when a person eligible for vaccination, and with no valid contraindication, visits a health service facility and does not receive all of the recommended vaccines. The number of MOV in some countries is huge, and globally the pooled prevalence of MOV was estimated at round 32% for children.⁵ With little effort or cost (compared with reaching children who have no access to the health system), ensuring that all

tionnelle à une gestion stratégique des approvisionnements; en explorant les avantages que peuvent présenter les achats groupés).

3. Une attention particulière a été portée à la nécessité de rationaliser les prescriptions réglementaires et les exigences applicables aux produits. Le SAGE a suggéré que des représentants des autorités réglementaires se réunissent pour réfléchir aux moyens de rendre le processus réglementaire plus souple et cohérent. Les organismes de réglementation supranationaux peuvent avoir un rôle à jouer en fournissant des conseils et un avis scientifique sur les produits non homologués aux organismes nationaux.
4. Le SAGE a indiqué qu’en sus de nouvelles activités, les stratégies à long terme visant à assurer la sécurité de l’approvisionnement en vaccins sont importantes et doivent se poursuivre.

Le SAGE a fait valoir que l’OMS peut jouer un rôle clé en créant un «forum d’échange» qui permettrait de recueillir les informations sur la demande provenant de tous les États Membres et améliorerait le dialogue entre les pays, qui feront connaître leur demande (y compris par anticipation des modifications de calendrier et des nouvelles introductions), et les fabricants, qui rendront compte de la disponibilité des produits et des risques d’approvisionnement. Le SAGE a reconnu que la capacité de l’OMS à assumer ce rôle dépend de la disponibilité des ressources financières, ainsi que de l’engagement de toutes les principales parties prenantes, comme la Division des approvisionnements de l’UNICEF, la Fondation Bill & Melinda Gates, l’Alliance GAVI, les fabricants de vaccins et les pays.

À titre de mesure immédiate, le SAGE a proposé qu’une communication efficace soit assurée pour informer les pays des causes des pénuries, des activités engagées pour en atténuer l’impact, ainsi que des stratégies adoptées à long terme. Cela donnerait aux pays l’assurance que le problème n’est pas ignoré, ce qui est particulièrement important étant donné l’impact reconnu des pénuries sur la confiance des communautés à l’égard des programmes de vaccination.

Occasions manquées en matière de vaccination

Préoccupé par la stagnation de la couverture vaccinale, le SAGE avait recommandé, dans le cadre de son examen du Plan d’action mondial pour les vaccins en 2014, que des études soient menées pour identifier les occasions de vaccination manquées par les agents de santé et leurs systèmes de suivi et définir les mesures qui permettraient d’en réduire le nombre.⁴ Le SAGE a pris connaissance de l’avancement des activités dans ce domaine et a été invité à approuver les éléments de la stratégie actualisée de réduction des occasions manquées en matière de vaccination.

On parle d’occasion manquée de vaccination lorsqu’une personne remplissant les conditions pour être vaccinée et ne présentant aucune contre-indication valable ne reçoit pas tous les vaccins recommandés lorsqu’elle se rend dans un établissement de soins. Dans certains pays, le nombre d’occasions manquées est énorme et à l’échelle mondiale, on estime que la prévalence globale de ces occasions manquées est de l’ordre de 32% chez l’enfant.⁵ Il suffirait de peu, en termes d’efforts et

⁴ See No. 50, 2015, pp. 561–579.

⁵ Sridhar, et al. A systematic literature review of missed opportunities for immunization in low- and middle-income countries. *Vaccine* 2014; 32:6870–6879.

⁴ Voir N° 50, 2015, p. 561–579.

⁵ Sridhar, et al. A systematic literature review of missed opportunities for immunization in low- and middle-income countries. *Vaccine* 2014; 32:6870–6879.

visitors to health centres are vaccinated can have a major impact on the coverage of national immunization programmes.

WHO has recently updated the protocol and tools for conducting MOV assessments, as well as the guidance for follow-up interventions. These components comprise: a Planning Guide outlining a 10-step process; a detailed MOV Assessment Protocol; an Interventions Handbook; and a Partner Coordination Framework to support the scale-up of the MOV strategy and amplify its impact. Together with WHO Regional Offices, MOV assessments have been undertaken in the Dominican Republic, Panama, Peru, Colombia, Chad and Malawi and are being planned in another 8 countries.

SAGE was presented with the MOV experiences from 2 regions (AFR and AMR) which showed compelling evidence that children attending health facilities for vaccination, clinical care or other reasons were not offered all of the recommended vaccines (57% for all clinic attendees, 25% for children attending for vaccination, and 89% among those attending for medical consultation). Reasons for MOV were mostly attributed to health-care workers (>60%), caregivers (27%) and health services (11%). Lack of integration of services was illustrated by the very high proportion of children attending for treatment who were not referred for vaccination. Related to this is the importance of vaccination records. Home-based records/child health cards in use can affect the ability to verify vaccination status (child health passports which must be brought to every clinic visit versus child vaccination cards used for immunization services only). A key feature of the MOV strategy is that data collection is designed to lead to action through the identification of locally appropriate solutions and the development of work plans to reduce MOV. To ensure sustainability these are accompanied by supervision and long-term impact monitoring of the use and impact of these tools.

SAGE strongly endorsed the components of the updated MOV strategy as a simple and concrete way to improve coverage, equity and timeliness of vaccination and seen as a substantial move forward with great potential impact, immediately applicable and to be promoted widely. SAGE urged other partners to join the MOV effort. Given its direct relevance to HSS, SAGE encouraged countries and partners to include interventions to reduce MOV in every HSS funding application and plan.

de coût (par rapport à la couverture des enfants sans accès au système de santé), pour assurer la vaccination effective de toutes les personnes se présentant dans les centres de soins, mais l'incidence qu'aurait une telle initiative sur la couverture des programmes nationaux de vaccination serait considérable.

L'OMS a récemment actualisé le protocole et les outils utilisés pour l'évaluation des occasions manquées, ainsi que ses orientations sur les interventions de suivi. Les instruments concernés sont les suivants: un guide de planification comprenant un processus en 10 étapes; un protocole détaillé d'évaluation des occasions manquées de vaccination; un manuel sur les interventions; et un cadre de coordination avec les partenaires pour soutenir l'extension de la stratégie sur les occasions manquées de vaccination et en accentuer l'impact. En concertation avec les bureaux régionaux de l'OMS, des évaluations des occasions manquées de vaccination ont été menées en Colombie, au Malawi, au Panama, au Pérou, en République dominicaine et au Tchad, et d'autres sont prévues dans 8 autres pays.

Deux Régions (la Région africaine et la Région des Amériques) ont présenté au SAGE des données concernant les occasions manquées de vaccination, lesquelles indiquaient clairement que nombre d'enfants se présentant dans les établissements de santé, que ce soit pour être vaccinés, pour des soins cliniques ou pour toute autre raison, ne se voyaient pas offrir tous les vaccins recommandés (57% des enfants recevant des soins cliniques, 25% des enfants venus pour se faire vacciner et 89% des enfants se présentant pour une consultation médicale). Ces occasions manquées étaient dans la plupart des cas imputables au personnel soignant (>60%), aux personnes en charge des enfants (27%) et aux services de santé (11%). La très forte proportion d'enfants n'ayant pas été orientés vers les services de vaccination parmi ceux qui se présentaient pour un traitement témoigne du manque d'intégration des services. Il convient à cet égard de souligner l'importance des carnets de vaccination. L'utilisation de certains carnets ou fiches de santé tenus à domicile peut rendre la vérification du statut vaccinal de l'enfant difficile (passeports de santé de l'enfant, qui doivent être apportés à chaque visite clinique, par opposition aux carnets de vaccination destinés aux seuls services de vaccination). La stratégie sur les occasions manquées de vaccination se caractérise par le fait que la collecte des données est conçue pour déboucher sur des actions, s'appuyant sur l'identification de solutions localement adaptées et l'élaboration de plans de travail pour combattre le problème. Dans un souci de pérennité de ces actions, une supervision et une surveillance à long terme de l'utilisation et de l'impact de ces outils sont assurées.

Le SAGE a fermement soutenu les éléments de la stratégie actualisée sur les occasions manquées de vaccination, jugeant qu'ils offrent un moyen simple et concret d'améliorer le taux de couverture, l'équité et les délais de vaccination. Le SAGE estime qu'il s'agit d'une avancée substantielle, présentant un impact potentiel important et des possibilités d'application immédiate, qu'il convient de promouvoir largement. Le SAGE a vivement encouragé les autres parties prenantes à se joindre à cette initiative. Comme cet effort est directement lié au renforcement des systèmes de santé, le SAGE a invité les pays et partenaires à inclure des interventions de réduction du nombre d'occasions manquées de vaccination dans tous leurs plans et demandes de financement destinés au renforcement des systèmes de santé.

SAGE recommended increasing the pace of development of electronic immunization registry/recall/reminder systems given the widespread adoption of mobile phones and evolution of mHealth technologies even in resource-limited settings, ensuring highest level of data protection.

A key change in mind-set to address MOV could be to vaccinate children as a default response, and to treat every clinical presentation as a vaccination opportunity. Without a specific reason not to vaccinate (noting that lack of documentation is not a valid reason for not vaccinating), every child should be vaccinated.

Second-Year-of-Life immunization platform

Information was presented to SAGE on creating guidance for national programmes to establish routine healthy child visits during the second year of life (2YL). In recent years, WHO has substantially increased the number of recommended vaccines and made several recommendations of vaccinations beyond infancy. There are multiple benefits to establishing a strong platform for immunization and other interventions in the 2YL: (i) it provides an additional routine contact to deliver primary vaccination doses, booster doses (e.g. DTP) and second doses (e.g. measles-containing vaccine (MCV2)). For some newer vaccines such as pneumococcus and meningitis A vaccines, some schedule options include a routine dose in the 2YL; (ii) a strong platform in the 2YL provides an important opportunity for children to complete their vaccination schedule and to improve overall coverage; (iii) a routine visit creates opportunities to integrate multiple other evidence-based health interventions, and reinforces good Primary Health Care practice. The delivery of vaccines may act as an incentive for caregivers to attend a healthy child visit and obtain other health interventions such as vitamin A supplementation, nutrition, growth monitoring, and anthelmintic treatment.

The presentations outlined the planned projects to develop guidance and gathering experiences from Zambia and Senegal, and incorporating outcomes of related projects in Ghana. The history and challenges Zambia faced with the introduction of MCV2 were described, and the process followed in identifying shortcomings and defining additional strategies to improve programme delivery. Key deficiencies included that the introduction of MCV2 dose was viewed as “only” an additional dose of measles vaccine, not as establishment of a routine visit at 18 months of age, and less attention was paid to the training of health workers and the launch of this dose. It was compounded by an insufficient reminder system given the long gap between MCV2 and prior vaccination contacts, and confusion on eligibility for vaccination in the 2YL, including children who had missed doses in the first

Le SAGE a recommandé d'accélérer le développement de systèmes électroniques d'enregistrement et de rappel de vaccination, compte tenu de l'utilisation généralisée des téléphones mobiles et de l'évolution des technologies mobiles pour la santé (mHealth), même dans les contextes de ressources limitées, offrant le plus haut niveau de protection des données.

Pour réduire le nombre d'occasions manquées de vaccination, on peut envisager un changement de perspective fondamental, consistant à faire de la vaccination des enfants une intervention par défaut et à traiter toute présentation clinique comme une occasion de vaccination. S'il n'existe aucune raison spécifique de ne pas vacciner (l'absence de documentation ne constituant pas une raison valide de non vaccination), tous les enfants devraient être vaccinés.

Plateforme de vaccination pour la deuxième année de vie

Une présentation faite au SAGE a porté sur l'élaboration d'orientations destinées aux programmes nationaux concernant la mise en place de visites de contrôle régulières durant la deuxième année de vie. Ces dernières années, l'OMS a sensiblement accru le nombre de vaccins recommandés et a émis plusieurs recommandations sur la vaccination au-delà de la première enfance. L'établissement d'une plateforme robuste de vaccination et d'autres interventions dans la deuxième année de vie présente de nombreux avantages: i) cela permet un contact de routine supplémentaire pour l'administration des doses de primovaccination, des doses de rappel (par exemple DTC) et des secondes doses (par exemple vaccin à valence rougeole (MCV2)). Pour certains nouveaux vaccins, comme les vaccins contre les pneumocoques et la méningite A, le calendrier vaccinal peut prévoir une dose systématique dans la deuxième année de vie; ii) une plateforme solide dans la deuxième année de vie fournit une occasion importante de mener à bon terme toutes les vaccinations enfantines prévues au calendrier et d'améliorer la couverture vaccinale globale; iii) les visites de contrôle sont l'occasion d'intégrer plusieurs interventions sanitaires fondées sur des bases factuelles et de renforcer les bonnes pratiques de soins de santé primaires. L'administration des vaccins peut inciter les personnes s'occupant des enfants à se présenter aux visites de contrôle, l'enfant pouvant ainsi bénéficier d'autres interventions, comme une supplémentation en vitamine A, des conseils de nutrition, un suivi de la croissance ou un traitement anthelminthique.

Les projets prévus, consistant à formuler des orientations, à tirer les enseignements des expériences de la Zambie et du Sénégal et à incorporer les résultats de projets semblables menés au Ghana, ont été présentés. Cette présentation comportait une description de la chronologie de l'introduction du MCV2 en Zambie, des difficultés rencontrées lors de cette introduction, ainsi que du processus suivi pour identifier les carences et définir de nouvelles stratégies afin d'améliorer l'exécution des programmes. Les problèmes principaux avaient trait au fait que l'introduction du MCV2 était perçue comme consistant «simplement» en l'administration d'une dose supplémentaire de vaccin antirougeoleux, et non comme l'établissement d'une visite de contrôle à 18 mois, et une attention insuffisante a été portée à la formation des agents de santé et au lancement de cette dose. À cela est venu s'ajouter l'insuffisance du système de rappel, compte tenu de la longue période séparant l'administration du MCV2 des visites de vaccination précédentes, ainsi

year of life, and record keeping issues. The Zambian Ministry of Health initiated a process to address these challenges, focusing on the development of policies and guidelines, improvement of data collection and recording tools, assuring the availability of necessary commodities at the point of service delivery (including the non-vaccine commodities required to deliver a comprehensive healthy child service) and community engagement and communication.

The global landscape analysis and literature review provided insights into experiences from many countries on routine visits in the 2YL, highlighting the gap between doses given by the end of the first year of life and those delivered later. While many countries have introduced a 2YL visit, there is a large vaccination drop-out for doses given in the first year of life. Missed opportunities for catch-up are a major cause of lower 2YL coverage. Frequently vaccines are given at different times during the 2YL, and other health interventions are poorly integrated with the vaccination visit. SAGE strongly endorsed the importance of a fixed 2YL opportunity but emphasised that measures should be taken to ensure that health-care services were also developed to accommodate catch-up doses at other ages when opportunities arose through health-care contact.

SAGE endorsed the development of this guidance, noting that the work is strongly supportive of a comprehensive PHC approach with continuum of care, ensuring that the immunization service requirements are firmly embedded into a broader delivery of health services appropriate for this age group. The increasing complexity of the schedule requires better guidance to health workers on how to decide on eligibility for vaccines, especially for children who missed earlier doses. While WHO has developed recommendations to deal with “interrupted or delayed schedule”,⁶ countries should be supported to develop easy-to-understand job-aids or decision flow-charts to deal with such events, helping the health worker to make appropriate decisions. Recording and reporting tools should be revised to ensure that data are collected adequately, and that forms do not communicate false policy. The expansion of electronic vaccination registries would greatly facilitate the proper understanding and tracking of the programme in the 2YL. SAGE requested that the final guidance be reviewed by the Immunization Practices Advisory Group and then sent to SAGE for endorsement.

qu’une confusion quant aux critères d’éligibilité des enfants à la vaccination dans la deuxième année de vie, notamment lorsque des doses ont été omises durant la première année ou lorsque la tenue des dossiers de vaccination est inadéquate. Pour surmonter ces difficultés, le ministère de la santé zambien a amorcé un processus axé sur l’élaboration de politiques et de lignes directrices, l’amélioration des outils de collecte et d’enregistrement des données, la disponibilité des fournitures nécessaires sur le lieu de prestation des services (y compris les produits non vaccinaux nécessaires au bon déroulement d’une visite de contrôle complète), la mobilisation et la sensibilisation communautaires.

Une analyse de la situation mondiale et un examen de la littérature ont fourni un aperçu des expériences acquises par de nombreux pays concernant les visites de contrôle dans la deuxième année de vie, mettant en évidence l’écart existant entre les doses administrées à la fin de la première année de vie et les doses ultérieures. Bien que de nombreux pays aient institué une visite durant la deuxième année de vie, on observe un taux élevé d’abandon de la vaccination pour les doses administrées durant la première année de vie. Les occasions manquées de rattrapage contribuent de manière essentielle à la faible couverture dans la deuxième année de vie. Souvent, les vaccins sont administrés à différents stades de la deuxième année de vie et les autres interventions sanitaires sont mal intégrées à la visite de vaccination. Le SAGE a fermement soutenu l’institution d’une visite fixe durant la deuxième année de vie, mais a souligné que des mesures devront être prises pour veiller à la mise en place des services nécessaires pour permettre l’administration de doses de rattrapage à un âge autre que l’âge fixé si l’occasion s’en présente lors d’un contact avec le système de santé.

Le SAGE a appuyé l’élaboration de ces orientations, ajoutant que ce travail s’inscrit pleinement dans une approche globale des soins de santé primaires fondée sur la continuité des soins et permet une bonne intégration des exigences de vaccination dans les services de santé généraux pour cette tranche d’âge. La complexité croissante du calendrier vaccinal suppose de mieux conseiller les agents de santé pour qu’ils puissent décider de l’éligibilité des enfants à la vaccination, en particulier lorsque des doses antérieures ont été omises. L’OMS a formulé des recommandations sur la marche à suivre lorsque le calendrier de vaccination est interrompu ou retardé,⁶ mais doit également appuyer les pays dans l’élaboration d’aide-mémoires ou de diagrammes de prise de décision faciles à comprendre pour aider les agents de santé à prendre les décisions adaptées dans de telles situations. Une révision des outils d’enregistrement et de notification s’impose également pour garantir une collecte adéquate des données et veiller à ce que les formulaires utilisés ne renvoient pas à des politiques incorrectes. L’expansion des registres électroniques de vaccination serait d’un apport considérable pour assurer une compréhension et un suivi adéquats du programme pour la deuxième année de vie. Le SAGE a demandé que les orientations finales soient examinées par le Groupe consultatif sur les pratiques de vaccination avant d’être transmises au SAGE pour approbation.

⁶ See Table 3: Recommendations for Interrupted or Delayed Routine Immunization - Summary of WHO Position Papers; http://www.who.int/immunization/policy/immunization_routine_table3.pdf

⁶ Voir Tableau 3: Recommendations for Interrupted or Delayed Routine Immunization - Summary of WHO Position Papers; http://www.who.int/immunization/policy/immunization_routine_table3.pdf

Dengue vaccine

Worldwide, dengue is the most extensively spread mosquito-borne viral infection. It is caused by 4 related viruses (DENV 1-4). In the last 60 years, the incidence of clinical dengue cases reported to WHO has increased 30-fold, with a much increased geographic range and expansion from urban to rural settings. The objectives of the WHO Global Strategy for dengue prevention and control (2012–2020) are to reduce mortality and morbidity from dengue by 2020 by at least 50% and 25% respectively.⁷ The first dengue vaccine, CYD-TDV (Dengvaxia®), has now been licensed by several dengue-endemic countries in Asia and Latin America for use in persons aged 9–45 or 9–60 years, and is under regulatory review in several others.

SAGE reviewed the evidence generated from 2 large Phase 3 clinical trials, one conducted in 2–14 year-olds in 5 countries in Asia, the other in 9–16 year-olds in 5 countries in Latin America. Vaccine efficacy over 25 months from the first dose among 9–16 year-olds, using data pooled from both trials, was 65.6% (95% CI 60.7–69.9).⁸ The sub-group benefit profile is complex: vaccine efficacy varied by infecting serotype (higher protection against serotypes DENV 3 and 4 than DENV 1 and 2), age (higher protection in older children), and disease severity (higher protection against hospitalized and severe dengue), and notably serostatus at the time of vaccination (higher protection in participants who had already been exposed to dengue virus). Some level of protection was seen even after the first dose. In those children vaccinated at ages 2–5 years in Asia, a statistically significant increased risk of hospitalized dengue was seen in vaccine recipients in the third year after the first dose, though this dissipated in years 4 and 5. The biologic mechanism behind this increased risk is currently not understood but may be related to naïve vaccine serostatus and/or age. A significant increase in hospitalizations was not seen in those older than 5 years. No other safety signal has been identified.

SAGE was presented with the results of comparative mathematical modelling evaluations of the potential public health impact of CYD-TDV introduction. There was agreement across the different models that in high transmission settings, the introduction of routine CYD-TDV vaccination in early adolescence could reduce dengue hospitalizations by 10%–30% over a period of 30 years, representing a substantial public health benefit. The modelling predicted that the vaccine would be less beneficial in low transmission settings, due to the higher proportion of seronegative individuals, where the vaccine has limited protective effect.

Vaccin contre la dengue

La dengue est la maladie virale transmise par les moustiques dont la propagation est la plus forte dans le monde. Elle est provoquée par 4 virus apparentés (DENV 1-4). Au cours des 60 dernières années, l'incidence des cas cliniques de dengue notifiés à l'OMS a augmenté d'un facteur 30, la zone géographique touchée est devenue beaucoup plus vaste et la maladie s'est propagée des zones urbaines aux zones rurales. La Stratégie mondiale de lutte contre la dengue (2012-2020) de l'OMS vise à réduire la morbidité et la mortalité imputables à cette maladie d'au moins 50% et 25% respectivement d'ici 2020.⁷ Le premier vaccin contre la dengue, CYD-TDV (Dengvaxia®), est désormais homologué dans plusieurs pays d'endémie d'Asie et d'Amérique latine pour la tranche d'âge de 9-45 ans ou de 9-60 ans, et est actuellement examiné par les autorités réglementaires de plusieurs autres pays.

Le SAGE a étudié les données générées par 2 grands essais cliniques de phase 3, le premier réalisé auprès de sujets de 2 à 14 ans dans 5 pays d'Asie, et le second chez des personnes de 9 à 16 ans dans 5 pays d'Amérique latine. Selon les données regroupées à partir des 2 essais, l'efficacité du vaccin sur une période de 25 mois après la première dose chez les sujets de 9 à 16 ans était de 65,6% (IC à 95%: 60,7–69,9).⁸ Le profil d'efficacité selon les sous-groupes était complexe: l'efficacité du vaccin variait selon le sérotype responsable de l'infection (protection plus importante contre les sérotypes DENV 3 et 4 que contre les sérotypes DENV 1 et 2), selon l'âge (protection accrue chez les enfants plus âgés), selon la gravité de la maladie (protection accrue dans les cas de dengue sévère ou nécessitant une hospitalisation), et surtout selon le statut sérologique au moment de la vaccination (protection accrue chez les participants qui avaient déjà été exposés au virus de la dengue). Un certain degré de protection a été observé dès la première dose. Parmi les enfants qui ont été vaccinés à l'âge de 2 à 5 ans en Asie, une augmentation statistiquement significative du risque d'hospitalisation pour dengue a été observée dans la troisième année après la première dose, ce risque se dissipant au cours de la 4^e et de la 5^e année. Le mécanisme biologique responsable de ce risque accru n'est pas encore connu, mais pourrait être associé à un statut sérologique vaccinal naïf et/ou à l'âge. Aucune augmentation significative des hospitalisations n'a été constatée chez les sujets de plus de 5 ans. Aucun autre signal de sécurité n'a été identifié.

Le SAGE a pris connaissance des résultats d'analyses comparatives de modélisation mathématique de l'impact potentiel de l'introduction du CYD-TDV sur la santé publique. Les différents modèles parvenaient tous à la conclusion que dans les situations de forte transmission, l'introduction de la vaccination systématique par le CYD-TDV au début de l'adolescence pourrait réduire le nombre d'hospitalisations pour dengue de 10%-30% sur une période de 30 ans, présentant donc un intérêt majeur pour la santé publique. Selon les modèles, les avantages du vaccin seraient moindres dans les contextes de faible transmission en raison de la proportion accrue de personnes séro-négatives, chez lesquelles le vaccin a un effet protecteur limité.

⁷ Using 2010 as a baseline.

⁸ Post-hoc analysis.

⁷ Par rapport à 2010.

⁸ Analyse post-hoc.

SAGE recommended that countries consider introduction of CYD-TDV only in geographic settings (national or subnational) with high endemicity, as indicated by seroprevalence of approximately 70% or greater in the age group targeted for vaccination or other suitable epidemiologic markers. The vaccine is not recommended where seroprevalence is below 50%. Dengue vaccine introduction should be a part of a comprehensive dengue control strategy together with a communication strategy, well-executed and sustained vector control, the best evidence-based clinical care for all patients with dengue, and robust dengue surveillance.

Decisions about introduction require careful assessment at the country level, including consideration of local priorities, national and subnational dengue epidemiology, predicted impact and cost-effectiveness with country-specific hospitalization rates and costs, affordability and budget impact. WHO and partners should provide further technical support to countries pre- and post-registration, including to national regulatory authorities reviewing the registration file, and to assist ministries in country-level decision-making and post-introduction implementation and impact evaluation.

When CYD-TDV is introduced it should be administered as a 3-dose series given as a 0/6/12 month schedule. However, additional evidence is needed to identify minimal and maximal intervals between doses and determine whether simplified schedules may elicit equivalent or better protection. In particular, 1 or 2 dose initial schedules with or without later boosting should be evaluated. Because of the prolonged duration of the immunization schedule and to enable better outcome monitoring, countries should have systems in place for tracking vaccination.

Because of the safety signal of increased risk of hospitalized and severe dengue identified in the 2–5 year age group, CYD-TDV is not recommended for use in children under 9 years of age, consistent with current labeling.

The target age for routine vaccination should be defined by each country based on an assessment of dengue endemicity and programmatic feasibility of targeting particular age groups. For the most highly endemic settings (e.g. seroprevalence at 9 years of age of approximately $\geq 90\%$), 9 years of age is projected to maximize impact. In settings with seroprevalence at 9 years below 90% (but above 50%), 11–14 years of age may be preferable.

Co-administration safety and immunogenicity data for age-relevant vaccines (in particular HPV and TT) in the adolescent age group are currently unavailable. Because the risk of immunological interference due to co-administration of the live CYD-TDV with non-live vaccines is considered small, co-administration is permissible with these and other non-live attenuated vaccines.

Le SAGE a recommandé que les pays envisagent une introduction du CYD-TDV uniquement dans les zones géographiques (nationales ou infranationales) de forte endémicité, caractérisées par une séroprévalence d'environ 70% ou plus dans la tranche d'âge ciblée par la vaccination ou par d'autres marqueurs épidémiologiques adaptés. Le vaccin n'est pas recommandé dans les zones où la séroprévalence est inférieure à 50%. L'introduction du vaccin contre la dengue doit s'inscrire dans une stratégie globale de lutte contre la dengue comprenant un plan de communication, des activités efficaces et soutenues de lutte antivectorielle, la prestation d'excellents soins cliniques reposant sur des bases factuelles pour tous les patients atteints de dengue et une surveillance solide de la maladie.

Les décisions relatives à cette introduction doivent reposer sur une évaluation minutieuse de la situation au niveau de chaque pays, en tenant notamment compte des priorités locales, de l'épidémiologie nationale et infranationale de la dengue, de l'impact attendu et du rapport coût-efficacité escompté compte tenu des taux d'hospitalisation et des coûts propres au pays, de l'accessibilité financière et de l'incidence budgétaire. L'OMS et ses partenaires devront fournir un soutien technique supplémentaire aux pays avant et après l'homologation, notamment pour appuyer les autorités nationales de réglementation dans l'examen des dossiers d'homologation et soutenir les ministères dans la prise de décision au niveau national, la mise en œuvre après l'introduction et l'évaluation de l'impact.

Lors de son introduction, le CYD-TDV devrait être administré selon un schéma à 3 doses, à 0, 6 et 12 mois. Cependant, il faudrait disposer de données supplémentaires pour identifier les intervalles minimaux et maximaux entre les doses et déterminer si des calendriers simplifiés sont susceptibles de conférer une protection équivalente, voire meilleure. Il convient en particulier d'évaluer des calendriers prévoyant l'administration initiale de 1 ou 2 doses, avec ou sans dose de rappel. En raison de la longueur du calendrier de vaccination et pour assurer une meilleure surveillance des résultats, les pays doivent disposer de systèmes permettant un suivi de la vaccination.

Compte tenu du signal de sécurité identifié dans la tranche d'âge de 2 à 5 ans, indiquant un risque accru de dengue sévère et d'hospitalisation, le CYD-TDV n'est pas recommandé pour les enfants de moins de 9 ans, conformément à l'étiquetage actuel.

L'âge cible de la vaccination systématique doit être défini par chaque pays à partir d'une évaluation de l'endémicité de la dengue et de la faisabilité programmatique de la vaccination chez des groupes d'âge particuliers. Dans les situations où l'endémicité est la plus forte (par exemple une séroprévalence à 9 ans s'élevant à environ $\geq 90\%$), on estime qu'une vaccination à l'âge de 9 ans devrait avoir un impact maximal. Dans les contextes où la séroprévalence à 9 ans est inférieure à 90% (mais supérieure à 50%), il peut être préférable de cibler la tranche d'âge de 11 à 14 ans.

On ne dispose actuellement pas de données d'immunogénicité et d'innocuité relatives à la coadministration de ce vaccin avec les vaccins pertinents (en particulier le vaccin contre le PVH et l'anatoxine tétanique) chez l'adolescent. Les risques d'interférence immunologique liés à l'administration concomitante du CYD-TDV vivant avec des vaccins non vivants étant jugés faibles, la coadministration avec ces vaccins et d'autres vaccins atténués non vivants est acceptable.

CYD-TDV has not been studied as an intervention for dengue outbreak control. Vaccination is not expected to impact the course of an ongoing outbreak. Any use of the vaccine during an outbreak should only be done in areas that meet the recommended criteria for routine vaccine introduction.

There are insufficient data on the use of CYD-TDV in pregnant and lactating women for SAGE to recommend use in this population. However, the limited data on inadvertent pregnancies collected during the clinical trials have yielded no evidence of harm to the fetus or pregnant woman. Women of child-bearing age who are targeted for vaccination do not need to be tested for pregnancy.

Until data become available from forthcoming studies in HIV-infected individuals, SAGE is not recommending the use of CYD-TDV in immunocompromised individuals. SAGE does not specifically recommend vaccination in travellers or health-care workers.

There are important research and implementation questions that remain for CYD-TDV. Research to better understand options for reduced or condensed dosing schedules, and safety in pregnant women are high priorities. Epidemiologic metrics based on high-quality age-stratified surveillance are needed to infer likely seroprevalence by age in order to target vaccination efforts. Phase 4 studies on vaccine effectiveness by dose, duration of protection, and long-term impact are also priorities. SAGE noted that using surveillance data to monitor population impact of a vaccination programme may be challenging as the year-to-year variability in dengue transmission may be greater than the expected vaccine impact. Long-term monitoring for severe dengue, in particular in seronegative vaccinated subjects, should be done in selected areas.

Surveillance should be strengthened, particularly for emerging infections with clinical similarities to dengue, such as Zika virus, arising in areas of the world where data are scarce or absent. Use of harmonized case definitions is encouraged to enhance data sharing and comparability across regions. ■

Aucune étude n'a été menée sur l'utilisation du CYD-TDV à titre d'intervention de riposte en cas de flambée de dengue. On estime que la vaccination ne devrait pas avoir d'incidence sur l'évolution d'une flambée en cours. L'utilisation du vaccin en situation de flambée doit se limiter aux zones satisfaisant les critères recommandés pour l'introduction du vaccin dans le programme de vaccination systématique.

On ne dispose pas de données suffisantes sur l'utilisation du CYD-TDV chez les femmes enceintes ou allaitantes pour permettre au SAGE de le recommander dans cette population. Toutefois, les données limitées sur les grossesses non intentionnelles recueillies durant les essais cliniques n'ont révélé aucun préjudice pour le fœtus ou la femme enceinte. Il n'est pas nécessaire de faire subir des tests de grossesse aux femmes en âge de procréer visées par la vaccination.

En attendant les résultats d'études à venir chez les sujets infectés par le VIH, le SAGE ne peut préconiser l'utilisation du CYD-TDV pour les personnes immunodéprimées. Le SAGE ne recommande pas expressément la vaccination des voyageurs ou des agents de santé.

D'importantes questions persistent concernant la recherche sur le CYD-TDV et la mise en œuvre de la vaccination. Une priorité élevée doit être accordée à la recherche pour mieux comprendre les possibilités de réduction ou de concentration du calendrier vaccinal et évaluer la sécurité du vaccin chez la femme enceinte. Il importe de disposer de mesures épidémiologiques fondées sur une surveillance de qualité stratifiée selon l'âge pour déterminer la séroprévalence probable selon l'âge, ce qui permettra de mieux cibler les efforts de vaccination. On accordera aussi la priorité à la conduite d'études de phase 4 sur l'efficacité vaccinale selon la dose, sur la durée de la protection et sur l'impact à long terme de la vaccination. Le SAGE a indiqué que l'utilisation des données de surveillance pour suivre l'incidence des programmes de vaccination sur la population peut présenter de réelles difficultés, la variabilité de la transmission de la dengue d'une année à l'autre pouvant être plus importante que l'impact attendu du vaccin. Un suivi à long terme des cas de dengue sévère, en particulier chez les sujets séronégatifs vaccinés, est recommandé dans certaines zones.

Il importe en outre de renforcer la surveillance des maladies, en particulier des infections émergentes présentant des similitudes cliniques avec la dengue, comme la maladie à virus Zika, survenant dans des régions du monde où les données sont rares ou inexistantes. Il est recommandé d'employer des définitions de cas harmonisées pour favoriser l'échange et la comparabilité des données entre les régions. ■

How to obtain the WER through the Internet

- (1) WHO WWW server: Use WWW navigation software to connect to the WER pages at the following address: <http://www.who.int/wer/>
- (2) An e-mail subscription service exists, which provides by electronic mail the table of contents of the WER, together with other short epidemiological bulletins. To subscribe, send a message to listserv@who.int. The subject field should be left blank and the body of the message should contain only the line subscribe wer-reh. A request for confirmation will be sent in reply.

Comment accéder au REH sur Internet?

- 1) Par le serveur Web de l'OMS: À l'aide de votre logiciel de navigation WWW, connectez-vous à la page d'accueil du REH à l'adresse suivante: <http://www.who.int/wer/>
- 2) Il existe également un service d'abonnement permettant de recevoir chaque semaine par courrier électronique la table des matières du REH ainsi que d'autres bulletins épidémiologiques. Pour vous abonner, merci d'envoyer un message à listserv@who.int en laissant vide le champ du sujet. Le texte lui-même ne devra contenir que la phrase suivante: subscribe wer-reh.

SAGE TRACKING RECORD OF RECOMMENDATIONS AND ACTION POINTS

SAGE recommendations are reflected in the SAGE tracking sheet. The "Recommendations/Action item" column reflects the specific recommendation made by SAGE. The "Meeting Date" column displays the date of the SAGE meeting during which the recommendation was originally made. The "Status" column indicates whether the work is currently ongoing, pending or completed.

Each recommendation has an appointed WHO focal point (not displayed in SAGE Yellow Book). The focal points are requested to update their recommendation in advance of each SAGE meeting and report on progress towards the recommendation in the "Comments and Follow Up" column.

When the recommendation is finalized, it is displayed as "Completed" in the SAGE yellow book. This item is then included in the SAGE Yellow Book for one additional SAGE meeting. After, the completed item is archived. Archived recommendations are no longer displayed in the SAGE Yellow Book but may still be accessed upon request to the SAGE secretariat. Therefore, the online tracking sheet provides a historical record of all SAGE recommendations and the Yellow Book displays the current recommendations.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
General	SAGE recommended strengthening national vaccination programs, integrating health services and strengthening health systems to promote universal health coverage.	Apr 2013	Ongoing	A teleconference was held on May 13 2013 with J. Abramson, P. Figueroa, and N. Arora and EPI (M. Zaffran and T. Goodman) to discuss the issue and provide briefing on the integration activities that historically and presently EPI is working on. Subsequently, in early June a draft typology was produced and shared that summarizes this area of work. The topic was discussed at the April 2014 SAGE meeting. SAGE concluded that addressing integration, by its very nature, requires a broader discussion beyond SAGE. In this regard, it was proposed that the SAGE working group on the Decade of Vaccines (DoV) consider options for moving forward, as integration is reflected as both a guiding principle and a strategic objective of the Global Vaccine Action Plan (GVAP). The Department secured funding at the end of 2014 to establish a position dedicated to the issue of integration. Recruitment has been completed and the recruited staff started in October 2015. At the April 2016 SAGE meeting, session on 'Implementation in the context of health system strengthening (HSS) and universal health coverage' was held. It was proposed that improvement of immunization services within the broader health services should be a third dimension of vaccine programmes alongside safety and effectiveness.
General	SAGE called for the identification of novel communication strategies for the work of GACVS to have a greater impact and help maintain confidence in vaccines.	Apr 2014	Completed	A review paper on the Global Advisory Committee on Vaccine Safety (GACVS) future is published: Asturias EJ, et al. Contributions and challenges for worldwide vaccine safety: The Global Advisory Committee on Vaccine Safety at 15 years. Vaccine. 2016 Jun 17;34(29):3342-9.
General	A recommendation was made for consideration of a platform for immunization coverage in the 2nd year of life, in view of potential necessary booster doses and opportunities to catch up with incomplete vaccination, and removing the artificial barrier often experienced after the 1st birthday.	Apr 2014	Ongoing	The second country case study of Senegal (after Zambia, which was presented to SAGE in April 2016) is under way and will feed into the development by JSI of the generic guidance of establishing a 2YL platform for delivery of vaccinations and other health interventions.
General	SAGE recommended that ways to improve curricula for medical personnel should be explored.	Nov 2008	Ongoing	This area of work has been stalled as the main person steering this work retired 2 years ago. AFRO has not been able to find a replacement for capacity building work. Only limited work has been happening in other regions in this area, also due to limited staff capacity.
General	SAGE stressed that additional disaggregation was needed in the analysis of the progress achieved on the ground, and in identifying bottlenecks for progress, and recommended that reports display disparities observed at sub-national levels.	Apr 2015	Ongoing	WHO HQ is working closely with regional offices to obtain subnational level data. Surveillance data for measles and rubella as well as for new vaccines is collected on district level on regular basis and there are efforts to collect sub-national level coverage data. Currently this is happening in AFR on monthly as well as annual basis; and in SEAR and EUR on, it is done on annual basis. In October 2016, at the Global monitoring meeting, discussion will take place about collecting this information annually from all regions and regular consolidation and dissemination.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
General	SAGE requested that a paper be developed, highlighting the circumstances under which off-label use of any vaccine can be recommended, while clarifying the differences between regulatory decisions and public health recommendations. Legal and programmatic implications of off-label recommendations and the need for clear communication should be considered.	Apr 2012	Ongoing	Advice was sought from the Expert Committee on Biological Standardization (ECBS), and added to the agenda of meeting on 15-19 October 2012. SAGE had previously requested a paper that highlights the circumstances in which off-label use of any vaccine could be recommended, while clarifying the differences between regulatory decisions and public health recommendations. During the November 2012 SAGE meeting, SAGE further requested ECBS to prepare guidance for national regulatory authorities on studies needed to support evidence-based, off-label use of vaccines which would benefit public health. It was noted that for regulators, product specific data are paramount. SAGE requested that an additional document to be prepared to advise the national immunization technical advisory committees about the type of data that might support a policy recommendation to use a vaccine outside its licensed schedule in order to achieve public health benefits such as operational simplicity or cost savings. Guidelines on procedures and data requirements for changes to approved vaccines were adopted by ECBS in October 2014 (TRS 993, annex 4). Preliminary consultations took place around the 2015 ECBS meeting for specific guidance on Labelling information of inactivated flu vaccines for use in pregnant women. This document is subject to public consultation until 19 February 2016 and it is hoped that the document will be finalized during the October 2016 ECBS meeting which is taking place in parallel with the SAGE meeting. A paper clarifying the differences between regulatory decisions and public health recommendations was commissioned. Unfortunately, there were protracted delays in finalization of the publication. The paper was finally submitted for publication in April 2016 and acceptance of publication is still pending.
AEFI reporting	SAGE urged that efforts be pursued to enhance Adverse Events Following Immunization (AEFI) reporting worldwide.	Apr 2016	Ongoing	With GAVI support, 30 AFR countries have established work plans. A first analysis of the new GVAP indicator for AEFI monitoring has identified 84 member states that meet the recommended level of at least 10 AEFI cases reported per 100,000 surviving infants per year.
AEFI reporting	SAGE commented on the passive surveillance data from the Uppsala Monitoring Centre (UMC) and raised concerns that the safety signal detection was not undergoing appropriate peer review. SAGE concurred with GACVS on the need to increase collaboration and to implement a strong review process.	Apr 2016	Ongoing	The GACVS concluded that signals documented by the UMC provide useful information in monitoring the safety of vaccines from worldwide sources. It was proposed that a strengthened process of collaboration with UMC would allow use of the expertise on vaccine safety available within the GACVS and partner agencies for the review of this information before it is communicated to the network of pharmacovigilance centres and to vaccine manufacturers. This review should take into account the limitations of signal detection methods along with the reviews performed routinely by the FDA and EMA, given their extensive experience and access to more complete information with the ICSRs they receive and that may not all be shared with UMC. The GACVS Secretariat will liaise with UMC to identify mechanisms for such collaboration. UMC revised its signal assessment guideline in April 2015. In March 2016, UMC was recommended to establish a review group for the vaccine signals.
Agenda item	SAGE requested a discussion on the global shortage of vaccines at the next meeting.	Apr 2015	Completed	After some delay, a session on preempting and responding to vaccine shortages was held at the April 2016 SAGE meeting.
Decade of vaccines/GVAP	SAGE recommended that the 2016 GVAP assessment report be presented at the World Economic Forum in Davos where the Decade of Vaccines was launched.	Oct 2015	Ongoing	The recommendation made at the October 2015 SAGE meeting arrived too late to be included to the Davos 2016 agenda. Therefore, it has been agreed upon with DoV partner agencies to include at World Economic Forum in Davos in January 2017. It will allow us to share the 2016 mid-term SAGE assessment report and also to be able to include some inputs from both SAGE recommendations on MNTE and Measles-Rubella Elimination revised strategies (to be presented to SAGE in October 2016). This topic has been discussed with the B&MGF in June during which a principle agreement has been reached. A concept note detailing the objectives, message and format of a possible Davos session has been developed by WHO to engage the discussion. Next step is to agree with partners on the basis of this note so a formal process can be initiated.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Decade of vaccines/GVAP	The SAGE working group should continuously review the need for reformulation of the indicators or mechanisms for collection and reporting of data.	Nov 2012	Ongoing	The SAGE report of progress with the Global Vaccine Action Plan (GVAP) for 2015 was published online and is available at: http://www.who.int/immunization/global_vaccine_action_plan/en/ This report was tabled at the Executive Board in January 2016 and at the WHA in May 2016. Twenty five speakers, including 20 delegates from Member States, one observer (Chinese Taipei), three civil society organizations and Gavi, the Vaccine Alliance took the floor during the discussion on the Global Vaccine Action Plan. The SAGE GVAP working group meeting took place on August 31 - September 1 2016. Following this meeting, the SAGE DoV finalized its draft GVAP assessment report 2016, which has been included in the SAGE Yellow Book. SAGE members will have to review, discuss, possibly amend the report and then endorse its final version during a dedicated SAGE session on 19th October 2016.
Dengue	A SAGE dengue working group should be convened to revise the data and prepare recommendations to SAGE as clinical trial data is expected to be submitted to the regulatory authorities in early 2015.	Oct 2014	Closed	The SAGE Working Group on Dengue Vaccines was constituted and held monthly teleconferences. Two face-to-face meetings of the group were held 23-25 September 2015 and 10-11 February 2016. The SAGE session for decision took place on 14 April 2016. A revised WHO position paper on the use of Dengue vaccine was published in July 2016.
Dengue Vaccine	SAGE requested that future recommendations on dengue vaccine safety be linked to the dengue vaccine development strategy.	Apr 2012	Closed	SAGE and GACVS reviewed the evidence on the safety of the licensed dengue vaccine. SAGE recommendations were incorporated into the dengue vaccine position paper published in July 2016, which highlighted critical post-licensure safety studies to be undertaken to further inform the risk/benefit profile of the vaccine.
Ebola vaccines	Noting WHO's unique position to coordinate the development of Ebola vaccines, SAGE stressed the importance of transparent and prompt sharing of information on the trial protocols and data from the phase 3 clinical trials, and the need for a greater role for WHO in facilitating the sharing of information so that results between studies will generate the greatest benefit for policy decision-making.	Apr 2015	Ongoing	The paper published in the Lancet titled, "Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomized trial" was shared with SAGE members. The positive results of the trial prompted SAGE to schedule an extraordinary teleconference mid- August after the SAGE Ebola Working Group meeting to discuss the further steps and the possible need for a preliminary statement/recommendation from SAGE. The Working Group presented to SAGE in October 2015. Regulatory evaluation of the vaccine is currently ongoing. At this stage, there are no new peer-reviewed data and the trials are still ongoing. No new data from the clinical trials in West Africa is available. There is information regarding a Russian developed vaccine that was licensed in Russia, but despite WHO requests no data is available. The final Ring trial data will be available in the Fall of 2017.
Ebola vaccines	SAGE was asked to immediately establish a SAGE working group on Ebola vaccines and vaccination.	Oct 2014	Ongoing	The working group (WG) was established and has met regularly via teleconference. A face-to-face meeting of the WG took place on March 9 and 10, 2015. The WG reviewed the current epidemiological data on Ebola Virus Disease (EVD), the preliminary results of the phase 1 trials, the status of the phase 2 and 3 trials, and the preparations for the large scale deployment of vaccines. They also identified the scope of the recommendations and the key questions and data for formulating recommendations. The framework was presented to SAGE at the April 2015 meeting. The SAGE working group met again on August 19-20 in Geneva to review the available information and begin to start framing recommendations, based on the framework approved by SAGE in April 2015. The working group input was presented to SAGE at the October 2015 meeting. Currently, the Working Group is awaiting new evidence from the clinical trials and regulatory approval of the vaccine before revising the topic and issuing draft recommendations. The Secretariat has had interactions with the two WG co-Chairs. A teleconference of the WG is planned for 3 October, 2016 to discuss the new data and subsequently a decision will be made regarding a face to face meeting in the fall of 2017.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Hepatitis A	Long-term protection from single or 2-dose schedules should be regularly monitored by countries and reviewed by SAGE.	Apr 2012	Ongoing	<p>Post-market surveillance continues in Argentina and a detailed report on the recent epidemiological situation was provided to WHO in February 2016.</p> <p>In 2014, in the context of a localized outbreak in a border area, 8 potential breakthrough cases were identified. For 5 of them there is uncertainty about the vaccination status and/or conditions (cold chain) in which vaccination was administered. Seven of these cases are in the 5-9 age group (distributed throughout the period) and one in the 1-4 age group. This has resulted in an enhanced vigilance in the country.</p> <p>However, there is currently still no evidence of waning immunity and the situation is compatible with very high vaccine effectiveness. The situation continues to be investigated. Hepatitis A cases have remained low in 2014 and 2015. Although a reduction in hepatitis A rates was experienced in all age groups, there is an increasing proportion of the remaining cases occurring in persons > 14 years of age in the post vaccination period. Most of these represent non-vaccinated adolescents or adults that escaped HAV-infection in previous outbreaks. Regarding children with a confirmed HAV-acute infection, many are unvaccinated children arriving from Bolivia where HAV vaccine is not included in the regular calendar.</p> <p>As exemplified by the outbreak in San Martin, the risk persists in the population. 73% of HAV acute infection cases reported occurred in individuals over >10 years. All cases reported occurred in unvaccinated individuals. Both Colombia and Paraguay also introduced a single dose national immunization schedule for 1 year old children. Yearly review of the Argentinian surveillance data will continue as Argentina was the front runner country to introduce a 1 dose schedule with the inactivated vaccine. A third phase immunogenicity study is ongoing in Argentina, to assess long term protective antibodies in children more than 9 years following single dose vaccination. So far the results of the phase two study conducted in 2013 and with a median post-vaccination interval of 7.7 years have been quite reassuring with 97.4% (95% CI: 96.3-98.3) still protected. A proactive further follow-up will be done ahead of the April 2017 SAGE meeting.</p>

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Hepatitis B	SAGE recommended that the timely delivery of a birth dose of hepatitis B vaccine (that is, within 24 hours of birth) should be used as a performance measure for all immunization programmes. Reporting and monitoring systems should be strengthened to improve the quality of data on the birth dose.	Apr 2009	Ongoing	<p>A consultation on implementation of a new universal birth dose recommendation was conducted in December 2010 with special focus on countries with a high percentage of home births. Outputs include a monograph documenting the systematic review and best practices from the consultation. Immunization Practices Advisory Committee (IPAC) reviewed this work in early 2011 and again in April 2012, and endorsed the 2013 publication of 'Practices to Improve Coverage of the Hepatitis B birth dose vaccine.' From this, work is ongoing to develop field guidelines for scaling up Hepatitis B birth dose. The JRF and associated materials have been revised to improve reporting of birth dose with a particular focus in Western Pacific Regional Office (WPRO). The WHO/UNICEF estimate process was piloted in 2012 in WPRO and was applied globally for the first time to the 2013 JRF birth dose data. Analysis of timely birth dose data for 2008 shows no significant changes from 2006 analysis and the major issue is lack of data quality. A study of the cost of scaling up the birth dose by country has been completed, based upon previously published methodology estimating the cost of implementing the Global Immunization Vision and Strategy (GIVS) goals. In 2012, WPRO convened Expanded Program on Immunization (EPI) and Maternal and Child Health (MCH) managers from the five priority countries to jointly propose actions towards improving birth dose uptake.</p> <p>In Jan 2015 the African Regional Office (AFRO), and in March 2015 WPRO, held Hepatitis B birth dose consultations to improve birth dose coverage. In Feb 2015, An AFRO workshop on birth dose introduction was conducted in Brazzaville; this workshop included guidance on birth dose monitoring. An assessment of birth dose implementation has taken place in Sao Tome Principe in July 2015 and Nigeria in September 2015 and in the Gambia in December 2015. Senegal held a Hepatitis B birth dose training workshop in Dec and introduced birth dose in January 2016.</p> <p>Guidance for Hep B birth dose introduction was published on June 2016 ('Preventing Perinatal Hepatitis B Virus Transmission: A Guide for Introducing Hepatitis B Birth Dose Vaccination', available from: http://www.who.int/immunization/documents/general/ISBN9789241509831/en/).</p> <p>In May 2016, guidelines for introducing birth dose vaccination have been published and include a chapter on reporting and monitoring birth dose vaccination: http://apps.who.int/iris/bitstream/10665/208278/1/9789241509831_eng.pdf.</p> <p>In July 2016, a proposal to revise WHO/UNICEF Joint Reporting Form (JRF) report on birth dose was submitted (suggesting to report late and timely birth dose globally).</p>

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Hepatitis B	All regions and associated countries should develop goals for hepatitis B control appropriate to their epidemiologic situations. Serologic surveys of hepatitis B surface antigen (HBsAg) prevalence, representative of the target population, will serve as the primary tool to measure the impact of immunization and achievement of the control goals.	Nov 2008	Ongoing	In June 2016, the South East Asian Regional Office (SEARO)'s ITAG recommended to establish a Regional control goal of less than or equal to 1% HBsAg sero prevalence by 2020 among children aged 5 years. In August 2015, an HQ mission took place to discuss HepB control targets. In August 2016, the The African Regional Office (AFRO) Regional Committee discussed adopting a viral hepatitis strategy in line with the Global Health Sector Strategy (GHSS) for viral hepatitis which includes a hepatitis B control target in-line (although more ambitious) with the target endorsed as part of the immunization strategy at the 2014 RC meeting. In 2014, the AFRO RC meeting adopted resolution to reduce Hep B infection to <2% among children under 5 years of age by 2020 and adopted hepatitis B activities as part of the RVAP that was also endorsed at the same RC meeting. The Eastern Mediterranean Region (EMR) has a Regional Committee (RC) goal of reducing childhood hepatitis B prevalence to <1% among children <5 years by 2015. Its regional office, EMRO is working with Member States to ensure achievement of this goal. The Western Pacific Region (WPR) established a RC goal to reduce hepatitis B infection to <1% among children at least 5 years of age by 2017. The European Regional Office (EURO) will consider a regional hepatitis B control goal as proposed by ETAGE. The Pan American Health Organization (PAHO) has resolved to eliminate hepatitis B virus transmission and is formulating a regional strategy. Documenting the "Impact of Hepatitis B Immunization: best practices for conducting a serosurvey" (WHO/IVB/11.08) was published in 2011 by the department of Immunization, Vaccines and Biologicals. In 2012, WHO HQ has published a framework for global action to control viral hepatitis (http://www.who.int/csr/disease/hepatitis/Framework/en/index.html). The 2016 WHO Executive Board approved a global health sector strategy on viral hepatitis 2016-2021 that proposes an impact target of less than 1% HBsAg prevalence among children by 2020 and 0.1% by 2030.
HIV	SAGE requested regular updates on the progress of HIV-vaccine research.	Apr 2010	Ongoing	The anticipated start of a phase 2 efficacy trial in South Africa constitutes an important progress in the HIV vaccine research and development area, building on the promising results from the RV144 Phase 3 trial in Thailand (which showed 31 % protection against new HIV infection during the 3.5 years after vaccination, 60 % during the first year), and an ongoing preparatory study in South Africa. The vaccination regimen in the upcoming HVTN 702 trial in South Africa will, like RV144, be based on a canarypox-based vaccine called ALVAC-HIV and a bivalent gp120 protein subunit vaccine, but will also include a new adjuvant, target HIV subtype C and include the addition of booster doses. Other live-attenuated candidate vaccine constructs are under evaluation in early clinical development. Finally there are major, and promising, vaccine science initiatives underway to attempt to induce broadly neutralising antibodies through re-engineered antigens. These have a longer time frame, but raise the prospect of cross-clade protection.
Immunization in Humanitarian Emergencies	SAGE stressed the need for continuous efforts in strengthening vaccination in humanitarian crises including further updating of field vaccination guides.	Apr 2016	Ongoing	A stakeholder meeting was convened on 20 June 2016 on identifying challenges and resolving barriers to timely supply of affordable vaccines in humanitarian crisis situations with participation from WHO, UNICEF, MSF, Save the Children, UNHCR and others. On 10/11 October 2016, a follow-up meeting will be held to ensure finalization of documents in the making and follow up on the June meeting. Current work on specific documents in progress includes 1. updating of the framework for decision making; 2. facilitating the use of the framework by developing an operational manual plus related online-based tools; 3. developing an implementation guideline for use of vaccination in humanitarian emergency situations; and 4. developing appropriate communication and dissemination plan to ensure wide distribution of the package of tools.
Immunization schedules	SAGE requested that IVIR-AC assess optimal immunization schedules based on both direct and indirect effects and not only direct effects.	Oct 2015	Ongoing	As part of any vaccine impact evaluation, IVIR-AC reviews and encourages studies of optimal schedules on both direct and indirect effects. Study projects and meetings have been held and are planned on HPV, Hep B vaccines, rotavirus vaccines among others.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Immunization schedules	SAGE requested a critical appraisal of alternative schedules for pneumococcal conjugate vaccine, rotavirus vaccine and Hib vaccine in 2011.	Nov 2010	Ongoing	<p>Pneumococcal Conjugate Vaccine (PCV): evidence was reviewed by SAGE in November 2011. New recommendation on schedules was issued and data was used to update the position paper.</p> <p>Rotavirus: evidence was reviewed by an ad-hoc group of experts in February 2012 and presented to SAGE in April 2012. An updated vaccine position paper on the use of rotavirus vaccines was published in February 2013.</p> <p>Haemophilus influenzae type b (Hib): The issue was revised during the April SAGE 2013 meeting. New PP was issued.</p> <p>Pertussis vaccine was reviewed in 2015. New position paper was issued.</p> <p>Hep B vaccine will be reviewed in Oct 2016.</p> <p>HPV vaccine will be reviewed in Oct 2016.</p> <p>TT vaccine will be reviewed in Oct 2016.</p> <p>A systematic review of Diphtheria vaccines was conducted.</p> <p>For all: review of number of contacts during first years of life (ongoing); cost of contacts (planned); update on actual age at vaccination data (completed and used in conjunction with rotavirus epidemiology). Delays due to impact of Ebola outbreak on staff responsibilities.</p> <p>A consultation to develop an analytic tool to support countries with the selection and/or adjustment of vaccine schedules in different epidemiological and operational scenarios will take place in Dec 2016.</p>
Immunization Supply Chains	SAGE requested future update on approaches to prioritization within supply chain improvement plans.	Oct 2014	Completed	<p>Under the umbrella of the WHO-UNICEF Immunization Supply Chain and Logistics Hub, a process has started to implement the more holistic approach to immunization supply chain improvement planning as part of the WHO-UNICEF Joint Statement that was endorsed by SAGE. The approach builds on a methodology to prioritize strategies and activities that will have the largest impact on immunization supply chain improvements. In addition, evidence around cost-effective solutions is being compiled by the Hub which will be transformed into an Solutions Toolbox to help countries tailor and prioritize the right solutions.</p> <p>5 countries have developed a supply chain improvement plan - Pakistan, Democratic Republic of Congo, Lao People's Democratic Republic, Bangladesh, and Nepal.</p>
Immunization Supply Chains	SAGE recommended that the EVM assessment include the measurement of human resource capacity and encouraged WHO to use EVM assessments in alignment with new vaccine introduction impact assessments and to strengthen the links between supply chain issues and programme outcomes. To further improve the EVM assessment, it was suggested that the tool be used for supervisory purposes and that a composite score be developed to complement the across-the-board benchmark of 80%.	Apr 2014	Completed	<p>Under the umbrella of the WHO-UNICEF Immunization Supply Chain and Logistics Hub, a process has started to develop a revised version of the Effective Vaccine Management (EVM) assessment tool for it to become an assessment that covers broader immunization supply chain and logistics aspects beyond vaccine management policies and practise. Since this is a significant undertaking and a time consuming one, the approach in 2015 is to include additional data collection and/or assessment modules for Human Resources alongside the existing approach to EVM assessments. This Human Resource module is being developed by UNICEF Supply Division under the auspices of the People that Deliver (PtD) initiative, Gavi, and the People and Practise working group of the immunization supply chain taskforce. In addition, the revisions of the EVM assessment tool will include more supply chain performance measures and indicators that are more outcome oriented but aligned with the global key performance indicators being developed to track performance in countries with regards to the GAVI Supply Chain strategy.</p>

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Implementation	SAGE recommended the formation of an implementation group that had a broad array of expertise in this area.	Apr 2015	Ongoing	In April 2015, SAGE stressed the importance of applying the rigour and science in implementation programme design and evaluation of delivery of vaccines, in order to maximize the impact of current and future vaccines and delivery technologies. SAGE had further elaborated the above in a two page concept note. This document was then discussed within WHO. It was proposed and agreed upon by SAGE that instead of forming a SAGE working group, the Department of Immunization, Vaccines and Biologicals would first work with the Department of Health Systems Governance and Financing, which is involved with health systems strengthening (HSS), and the Department of Service Delivery and Safety group to organize a session on Implementation in the context of health system strengthening and universal health coverage at the April 2016 SAGE meeting. This session was successfully held. SAGE noted the advancements in knowledge in the field of HSS, which should support the attainment of immunization goals in a sustainable manner. The need to embed health systems thinking in every initiative and action, without losing goals so far attained, was appreciated by SAGE as a way forward. SAGE emphasized the importance of ensuring the visibility of immunization goals in planning HSS efforts. A system to generate data for evidence-based decision-making, with a focus on implementation research, is a route to achieving this. It was proposed that implementation research take up specific challenges that lead to strengthening of health systems. Improvement of immunization services within the broader health services should be a third dimension of vaccine programmes alongside safety and effectiveness, and this will need appropriate long term funding. SAGE recommended that WHO more actively promote further progress in this arena and that a preparatory team continue the dialogue and develop a more targeted agenda. For the time being it was concluded that no SAGE working group would be established, but that SAGE would be kept informed of meaningful developments.
Implementation	SAGE recommended that WHO promote further progress in the arena of implementation more actively, and that a preparatory team continue the dialogue and develop a more targeted agenda.	Apr 2016	Ongoing	WHO is currently implementing multiple WHA resolutions that mandate integration of disease-specific programs, using a HSS framework. This aims to seek universal immunization coverage as part of UHC. Within the Gavi sphere, the Alliance has committed to having HSS be the framework for each country, under which all Gavi grants will be managed as a single investment. This is captured in the new Country Engagement Framework, which WHO HIS/HGS has assisted the Gavi Alliance Partners and Gavi Secretariat in developing.
Implementation research	The implementation research agenda should define equity beyond traditional economic metrics such as social economic status gradients, to include other measures of inequity such as the multidimensional poverty index or impacts on marginalized populations. SAGE suggested that studies to examine the integration of immunization with other health interventions should be included in the implementation research agenda.	Nov 2013	Ongoing	This recommendation is now part of the new Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) agenda under research to minimize barriers and improve coverage of vaccines currently in use. Since 2014 research topics on the non-specific effects of vaccines, missed opportunities and community vaccine acceptance have been part of the agenda of IVIR-AC.
Implementation Research	SAGE outlined some considerations for IVIR-AC to include in their deliberations – assessment of the use of high quality randomized controlled trials where feasible (noting the substantial ethical and methodological challenges involved), with sufficient power to explore sex differences, and a priori defined and standardized immunological endpoints designed to answer the specific question of non-specific effects– and emphasized that future research should draw on a broad investigator pool and from a wide range of geographic locations using a standardized protocol.	Apr 2014	Ongoing	During the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) June 2015 meeting, IVIR-AC endorsed the designing of one or more protocols to assess the prospective non-specific effects of immunization on mortality. The work of the WHO Secretariat needs to be completed in preparing the protocols for the questions identified and trials outlined during the ad-hoc expert consultation of February 2016. These generic protocols would enable harmonized implementation of the trials across multiple settings. While further development of all the proposed trial designs is important, IVIR-AC recognizes that full evaluation necessitates a complete protocol. IVIR-AC will help inform decisions on feasibility and the selection of designs, and formulate questions.

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Implementation Research	SAGE identified the conditions necessary for pertussis resurgence and the effective strategies for prevention of resurgence as important topics for modelling research.	Apr 2014	Ongoing	<p>The June 2015 meeting of the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) meeting agreed on the plan for phase 1 of the comparison of pertussis models from Australia, England & Wales and the United States of America, which is meant to be a rapid assessment on the relative contributions of vaccine formulations, waning immunity, vaccine coverage and schedule to the observed pertussis resurgence in these countries. If successful, phase 2 offers further opportunities to test whether existing models are sufficiently robust to changes in factors such as demographics, spatial heterogeneity, immunity and contact matrices across multiple settings. In many countries using aP vaccine in the national immunization programme, aP vaccine is used in the private sector which represents a variable proportion of infant immunizations, so these complexities will need to be reflected when the models are extended to low and middle income settings.</p> <p>Phase 1 has been implemented and preparations are under development for Phase 2 and implementation will depend on funds being made available.</p> <p>Pertussis surveillance and laboratory capacity are still extremely poor in LMICs (particularly in Africa), and beyond the scope of the model comparison exercise to address. The committee noted that data are expected to be forthcoming through ongoing studies and follow-on analysis of maternal influenza trials, and strongly endorses the identification of further opportunities to add pertussis markers (primarily PCR on respiratory specimens) to studies such as Gavi- or the BMGF- supported vaccine impact studies.</p> <p>There were concerns that the opportunistic process by which the 3 models were identified may not have included all relevant parameters or modelling approaches. The feasibility of taking into account other models and parameters identified through a literature review and/or open call should be assessed, focusing on the main results of the different models for phase 1, and if they are interested to include them in phase 2.</p> <p>The work under Phase 1 has recently been completed by the modelers and will be shared with SAGE Chair soon for further follow up. Meanwhile the WHO burden of pertussis disease estimates have been updated by the WHO secretariat in collaboration with Hong Kong University.</p>
Integration	WHO should discuss and develop guidelines on how to fully integrate vaccination (GVAP) into the operation of all aspects of the health-care system and to reduce missed opportunities to vaccinate.	Oct 2014	Ongoing	<p>During the April 2016 SAGE meeting, SAGE members were successfully updated on the ongoing work in AFRO, PAHO and SEARO on using the missed opportunities for vaccination (MOV) strategy to facilitate the integration of immunization with other health services. Following the SAGE session, WHO has received multiple requests from countries for technical assistance to implement the MOV strategy in additional countries. Based on the two MOV assessments conducted in Chad and Malawi in 2015 (draft manuscripts prepared for peer reviewed journal submission), the package of methodology materials will be finalized by Q4-2016. These include: a planning guide, the assessment methodology (including the MOV protocol, sample questionnaires and generic field guides) and an intervention guidebook. Having strengthened the capacity of AFRO to implement MOV assessments (discussions with DRC, Nigeria, Mauritania and Kenya are ongoing), collaboration is now ongoing with SEARO where MOV assessments have been completed in Timor Leste (interventions are ongoing) and are being planned and supported in Indonesia and Cambodia. To establish a network of partners engaged in MOV, an informal coordination meeting was conducted in March 2016 to provide briefing on the process and outcomes of the recent country MOV assessments, share future plans and framework for implementation, and achieve consensus on a coordination mechanism for all MOV work among all partners. The second partner coordination call took place on June 30, 2016, to provide an update partners on the successful April SAGE session and to coordinate ongoing and future MOV activities.</p>

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IVIR-AC	IVIR-AC should seek linkages with the WHO Alliance for Health Policy and Health Systems Research as they might be useful in priority setting and discussions.	Oct 2014	Ongoing	<p>The Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) secretariat have had initial discussions with WHO staff of the Alliance for Health Policy and Health Systems Research (HPSHR) to update on the IVIR-AC deliberations in September 2014. Discussions for concrete steps for their involvement in vaccine implementation research are ongoing.</p> <p>The WHO Alliance for HPSHR will have a seat in the WHO Secretariat of the IVIR-AC. In addition, Initiative for Vaccine Research (IVR) was involved in a call for proposals issued by the WHO Alliance with financial support from Gavi and UNICEF on implementation research studies in low and middle income countries (LMICs) in 2015. Seven proposals have been selected for funding and being implemented with a one year timeline until 2016.</p> <p>A new funding proposal is being prepared for 2016-2017 with support from Gavi and UNICEF. New projects have been granted and a workshop on implementation research protocol development took place in August 2016.</p>
IVIR-AC	SAGE noted that a sub-group of IVIR-AC members and external subject experts should make recommendations on the types of prospective studies to assess the non-specific effects of vaccines.	Oct 2014	Ongoing	<p>An ad-hoc consultation on clinical trials for non-specific effects of vaccines (NSE) was held on 16-17 February 2016. Eighteen experts (including 3 IVIR-AC members) contributed to this consultation, whose main objectives were to reach a consensus on priority trial questions and to propose trial designs for each of the priority questions. Protocol synopses for the six different trials that the experts proposed were prepared for review and discussion at June 2016's IVIR-AC meeting.</p>
Japanese encephalitis	Guidance is needed on how to approach Japanese encephalitis (JE) vaccine impact assessments. This guidance should address surveillance data sources and analysis to measure JE vaccine impact, design of surveillance and special studies for impact measurement, JE laboratory diagnostics, and data collection and analysis for observational studies to measure vaccine effectiveness	Apr 2015	Ongoing	<p>The guidance document is now available on WHO website: 'WHO guide to measuring effectiveness and impact of Japanese encephalitis vaccination' (available at http://www.who.int/immunization/diseases/japanese_encephalitis/JE_effectiveness.pdf).</p>
Lower middle-income countries: sustainable adoption and financing for new vaccines	SAGE requested that WHO facilitate the establishment of a partnership among all relevant stakeholders to consider: pooled procurement; tiered pricing; greater transparency of pricing; and exploring the role that UNICEF, the Pan American Health Organization and foundations can have in assisting these countries with procuring and financing vaccines.	Nov 2010	Ongoing	<p>WHO set up a Middle Income Countries (MIC) Task Force in June 2014 with main immunization stakeholders (WHO, UNICEF, World Bank, Gavi Secretariat, BMGF, AMP, Sabin, Task Force for Global Health), which led to the creation of the "MIC strategy", presented at SAGE in April 2015. The strategy aims at improving sustainability of immunization programmes and access to vaccines in non-Gavi MICs. The MIC strategy is based on four pillars : i) Strengthening evidence-based decision-making; ii) Enhancing political commitment and ensuring financial sustainability of immunization programmes; iii) Enhancing demand for and equitable delivery of immunization services; and iv) Improving access to timely and affordable supply.</p> <p>The timeline for the strategy is up to 2020 to align with the GVAP timeframe and up to 2025 for a longer term horizon. In the longer term, the MIC strategy could provide a platform to ensure sustainability of Gavi's investments in fully self-financing countries.</p> <p>Following SAGE's endorsement of the strategy, the WHO Secretariat has led implementation efforts in collaboration with immunization partners. Missions have been conducted in Swaziland, Romania and Jordan by WHO and partners as part of the country engagement process encouraged by SAGE. Also, different small efforts to support countries to strengthen their procurement capacity have taken place. Some effort is being undertaken also in the area of decision making and hesitancy. Work on price transparency continues (V3P has now grown to include data from 50 countries). Despite these efforts, progress in implementation of the strategy is very slow due to lack of funding. As discussed at the April 2015 SAGE meeting, the partners would require US\$20M per year to fully implement the strategy.</p>

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Malaria	SAGE noted the utility of PPCs to developers and funders, and proposed that the opportunity for input into future PPCs at an early stage for any vaccine of public health importance could be included as part of SAGE's global public health mandate.	Apr 2013	Ongoing	Malaria Vaccine Preferred Product Characteristics are finalized and available on WHO website: (http://apps.who.int/iris/bitstream/10665/149822/1/WHO_IVB_14.09_eng.pdf). RSV Preferred Product Characteristics are now under development. In addition, two Ebola vaccine Target Product Profiles (TPPs) have been developed for reactive and prophylactic use, and these are available from WHO website: (http://www.who.int/immunization/research/target-product-profile/ebolavaccine/en/). A Zika vaccine TPP went through public consultation, and is now available on WHO website: (http://www.who.int/immunization/research/meetings_workshops/WHO_Zika_vaccine_TPP.pdf).
Malaria Vaccine	SAGE requested continued review of the planning of the pilot implementations and to receive regular updates on the results.	Oct 2015	Ongoing	The WHO position paper was published in January 2016. WHO is working to secure funding for the SAGE/MPAC recommended malaria vaccine pilot implementation programme. For resource reasons, WHO is seeking to proceed in 3 countries. SAGE/MPAC recommended 3 to 5. In June 2016, the Gavi board approved funding for the pilots of up to 50% (up to \$27.5 million for the first 4 years out of a total needed of \$55 million). Gavi indicated they could provide 1 to 1 matching funds meaning that alternative sources must be found for the other 50% if the pilots are to continue. On 5th September, the UNITAID board committed \$9.6 million for the first 4 years leaving a critical gap (as a further \$27.5 million was requested by WHO). WHO is now refining the budget to the minimum possible for 2 countries and is in discussions with potential funders to try to find a way forward. Unfortunately, given the current funding positions by major donor organizations, the future of the malaria vaccine pilots is in doubt.
Maternal immunization	SAGE recommended that WHO endorse the importance and ethical imperative of clinical trials in pregnant women for potentially life-saving interventions such as RSV vaccine (and future vaccines against other targets currently in development, such as group B streptococcal disease).	Apr 2016	Ongoing	WHO is promoting vaccine trials be conducted in pregnant women. Updated TRS guidance for vaccines includes a section on trials in pregnant women. WHO Draft Preferred Product Characteristics for Next Generation Influenza Vaccines includes advocacy for clinical trials in pregnant women. Also, IVR has supported two efforts evaluating the ethics of maternal immunization: 1) Beeler JA, Lambach P, Fulton TR, Narayanan D, Ortiz JR, Omer SB. A systematic review of ethical issues in vaccine studies involving pregnant women. Hum Vaccin Immunother. 2016 May 31;1-8. [Epub ahead of print] PubMed PMID: 7246403, and 2) Verweij M, Lambach P, Ortiz JR, Reis A. Maternal Immunisation: Ethical Issues. In press at Lancet Infectious Diseases. Both publications advocate for the ethical imperative of clinical trials in pregnant women.
Maternal Immunization	SAGE encouraged WHO to promote more implementation research to generate generalizable data on the best ways to integrate maternal immunization into routine antenatal care in low resource settings	Apr 2015	Ongoing	IVR is in the process of producing many implementation research tools and guidance regarding: 1) assessment of vaccine confidence/hesitancy in pregnant women; 2) maternal influenza immunization program costing tool; 3) guidance document to estimate the influenza economic burden of a country; 4) guidance document to estimate the cost effectiveness of influenza vaccines in a country; 5) field guide for the evaluation of influenza vaccine effectiveness; 6) maternal immunization AEFI surveillance guidance; and 7) implementation guidance document. IVR is collaborating with the US CDC to pilot some of these tools in LMICs.
Maternal Immunization	SAGE concluded that the recommending bodies, including WHO, need to engage in a dialogue with regulators and manufacturers to review current regulatory practices against the evidence on risks and benefits and biological plausibility on product safety. SAGE requested WHO to develop a process and a plan to move this agenda forward in support of an increased alignment of data safety evidence, public health needs and regulatory processes.	Nov 2013	Ongoing	WHO is supporting evaluations of product monograph language regarding safety and use during pregnancy, as well as a survey of health care provider's perceptions of the specific product monograph language regarding use in pregnancy. WHO has reviewed various regulatory approaches to labelling of the pregnancy and lactation sections of product inserts, and it has convened several meetings on the subject: a consultation at WHO in July 2014 and a session at a meeting of the Developing Country Vaccine Regulators' Network (DCVRN) in China in November 2014. In collaboration with multiple NRAs globally, WHO has produced a draft guidance document titled, "Labelling information of inactivated influenza vaccines for use in pregnant women." The document is currently available for public comment. It will be revised to reflect the public consultation and reviewed by ECBS in late 2016.

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Maternal Immunization	SAGE encouraged the Regional Office for the Americas to document the successful regional experience of delivering influenza vaccine to pregnant women.	Apr 2015	Ongoing	Regarding PAHO/WHO's documentation of the successful regional experience of delivering influenza vaccines to pregnant women, PAHO has progressed significantly: - We have submitted a manuscript describing influenza uptake in the LAC region since the pandemic, highlighting the improvements in targeting pregnant women for vaccination in 29 countries. - During 2015 PAHO conducted, a survey among 14 LAC countries that aimed at describing the process from vaccine introduction decision, to implementation among pregnant women. It also tackled obstacles and enabled vaccine promotion and uptake. - In order to complement this survey, we are planning another in-depth survey to develop case-studies with key countries that have acquired a lot of experience in maternal immunization. As part of these case-studies, countries will share lessons learned. - PAHO convened a multi-disciplinary, inter-institutional working group to develop a field guide for maternal immunization which is in its finalization phase. This field guide targets EPI managers, EPI staff, and other healthcare workers involved in maternal and child health care. It should be published during 2016.
Measles	SAGE recommended further clinical, immunological, epidemiological and modelling studies regarding the impact of different measles vaccination schedules.	Oct 2015	Ongoing	The RIVM in the Netherlands (the same group that did the systematic review of use of measles vaccine under 9 months of age) will have results from their clinical studies of the immune response to an early dose of MMR vaccine by end of 2016. Modeling work is being done at US CDC to explore the effect of different vaccination schedules on the epidemiology of measles. An update on this work will be provided to the SAGE MR Working Group by end of 2016.
Measles	SAGE requested evidence on the need for measles revaccination of HIV-infected adolescents and adults. Further research is needed to monitor the long-term immune responses to measles vaccine in HIV-infected children revaccinated after starting HAART and in HIV-infected children starting HAART prior to receiving their first dose of MCV.	Oct 2015	Ongoing	Compiling the evidence on the need for measles revaccination of HIV-infected adolescents and adults was on the 2016 work plan of the SAGE Measles and Rubella Working Group (SAGE MR WG). Professor William Moss at Johns Hopkins University is taking the lead on this work. Research on the long-term immune responses to measles vaccine in HIV-infected children revaccinated after starting HAART needs to be taken up by clinical research groups.
Meningococcal A conjugate vaccine	SAGE recommended that countries completing mass vaccination campaigns introduce meningococcal A conjugate vaccine into the routine childhood immunization programme within 1–5 years following campaign completion, along with a one-time catch-up campaign for birth cohorts born since the initial mass vaccination and which would not be within the age range targeted by the routine immunization programme.	Oct 2014	Ongoing	The recommendations from SAGE are reflected in an update to the WHO meningococcal vaccine position paper. The updated guidance has been published in the Weekly Epidemiological Record WER on 20 February 2015: http://www.who.int/wer/2015/wer9008/en/ . Eight of the 26 meningitis belt countries have received approval from Gavi, the Vaccine Alliance for introduction of the meningococcal A conjugate vaccine into their routine immunization programme, with a single dose at 9, 15 or 18 months of age concomitantly with the administration of the first or second dose of Measles/Rubella vaccine. Among them, one country (Sudan) has launched their introduction at the age of 9 months in July 2016, another 2 countries (Ghana and Mali) will do so in November 2016 and the remaining 5 countries (Burkina Faso, Central African Republic, Chad, Niger and Nigeria) intend to do so in 2017. Other meningitis belt countries intend to apply for the introduction of the vaccine into their routine programme at the next Gavi application windows in September 2016 or in 2017.
Middle Income Countries Strategy	SAGE called upon WHO Secretariat to report back on progress in implementation of the Middle Income Strategy.	Apr 2015	Pending	WHO will work on the implementation of the MIC strategy and will report back to SAGE in October 2016.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Multiple injections	SAGE noted the need for further research on multiple injections during the same visit and recommended the following research topics and activities: (i) impact of multiple injections in the same visit on vaccine coverage, disease reduction, vaccine programme success and caregiver and provider experience; (ii) development of a standardized monitoring protocol for acceptance and acceptability by caregivers and providers and for prevalence of adverse events; (iii) development of optimal provider and infant caregiver communication approaches; (iv) optimal multiple injection administration techniques, and (v) development of new technologies, such as intradermal patches and new combination vaccines, which would decrease the number of vaccine injections in a single visit.	Apr 2015	Ongoing	A multiple injection study is being conducted in Nepal in collaboration with US CDC to evaluate healthcare provider and infant caregiver attitudes and practices regarding administration of multiple injectable vaccines in the same visit following introduction of IPV and PCV. A separate work stream in WHO IVB, in conjunction with WHO EMP and external partners (PATH, AMP), is investigating the development of microarray patch technologies with IPV and MR with special emphasis on Preferred Product Characteristics, relevant regulatory pathways and country health worker and caregiver acceptability. A BMGF RFP to support preclinical development of Measles-Rubella microarray patches is about to be published.
Pain mitigation	SAGE recommends that WHO: 1) includes pain mitigation recommendations with WHO immunization practice guidance materials; 2) disseminates pain/distress mitigation recommendations through the usual dissemination channels, immunization managers, National Immunization Technical Advisory Group (NITAG) and partner organizations; 3) monitors and evaluates the implementation success of pain mitigation measures; 4) works with industry, ECBS and regulatory agencies to advocate that grading of pain experienced during the vaccine injection be included in data for licensing and in the product monograph.	Apr 2015	Ongoing	<p>Internal discussions have taken place on how to move forward across relevant WHO departments. A brief position paper was drafted based on the SAGE recommendations and published in the Weekly Epidemiological Record on 25 September 2015. This formed the basis for additional proactive communication activities.</p> <p>As example of actions in response to points 1 and 2, WHO ensured that information in WHO guidance on multiple injections and IPV was consistent with the SAGE recommendations on reducing pain, specifically in two documents: Practical considerations for the successful introduction of IPV, and Multiple Injections: Acceptability and Safety, both available on this web page. The PP on reducing pain was also added on the same web page.</p> <p>In relation to the training aspects for IPV introduction, we updated training modules for health workers, also to reflect the recommendations from the latest PP. The Immunization in Practice recently published has in module 5 'Managing immunization sessions', recommendations on vaccine sequence (increasing pain- oral before injection, rota before OPV), positioning the recipient, no aspiration etc. IIP will be widely distributed to countries and the last edition was also translated into several local languages.</p> <p>Work is also ongoing to ensure appropriate incorporation of pain mitigation in WHO guidance documents when they get updated and to ensure that any recommendation posted on the web at odds with SAGE's guidance be adjusted/removed. The pain mitigation guidance has been included in the NITAG resource center. PDVAC will consider pain mitigation within their preferred product characteristics to guide target product profiles and include the topic in their envisage Vaccine special issue on the PDVAC pipeline analyses for 25 pathogens. Steps have been taken and discussions started to also reflect the measurement of pain at time of injection in the updated Guidelines on clinical evaluation of vaccines to be discussed and endorsed by ECBS in October 2016. More specific activities still need to be implemented with respect to points 3 and 4.</p>

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Polio	SAGE recommended working closely with countries on activities towards type 2 oral polio vaccine (OPV2) withdrawal.	Apr 2013	Completed	<p>In January 2014 a joint letter to all oral polio vaccine (OPV)-only using countries was sent by the WHO Director General and UNICEF Executive Director, and the Gavi CEO where applicable, highlighting the importance of inactivated polio vaccine (IPV) introduction and outlining the SAGE recommendation on IPV introduction schedules and planning timelines.</p> <p>This was followed up in May 2015 with a joint letter from the DG and UNICEF ED to all tOPV using countries on the importance of planning for the switch. All regions have held, at least one meeting that included a substantive focus on IPV introduction in 2014/5 and have held the same on the tOPV to bOPV switch in 2015. Joint WHO/UNICEF regional coordination mechanisms were established to ensure countries are suitably supported in the decision making process and in the development and implementation of introduction plans for IPV and the switch.</p> <p>Work was conducted in 2015 to i) ensure that declared intent materializes into commitment and ii) countries with no plan developed for the switch have one ready before the end of the year. In alignment with the SAGE April meeting discussions and the WHO resolution on the Switch, technical materials and standard operating procedures (SOPs) have been developed to accelerate switch planning at country level and have been shared with countries through regional consultations.</p> <p>Planning for the Switch was conducted in an accelerated manner with substantial technical assistance provided to countries through Partners and Regional offices. Financing was also be provided to high risk countries. A full update was be provided to SAGE in April 2016 as the Switch took place at about that time. A special tracking effort has been undertaken to ensure that no country falls between the cracks. As of the start of May 2016, all 155 countries and territories were no longer using the trivalent oral polio vaccine (tOPV).</p>
Polio	SAGE emphasised that UNICEF Supply Division, PAHO Revolving Fund and WHO should secure the global supply of prequalified bOPV.	Oct 2015	Closed	<p>OPV supply through the switch was considered sufficient for both tOPV as well as bOPV to ensure timely switch of the vaccines in routine vaccination programmes for countries procuring through UNICEF.</p> <p>The additional award made for 70 mds tOPV has allowed Pakistan to adjust its plans and to add more tOPV to the calendar and ensured sufficient supply to meet VDPV2 outbreaks in Myanmar and Lao. Countries procuring through UNICEF were on track for procurement of bOPV to introduce the vaccine in routine programmes after the switch, and are expected to continue to have sufficient bOPV supply after the switch.</p> <p>Demand forecasts were under review with the Vaccine Supply Task Team to ensure OPV supply was available in sufficient quantities. It was concluded that bOPV supply is available for 2017 and beyond.</p>
Polio	SAGE requested the Polio Working Group to evaluate options for catch-up vaccination for cohorts born after 1 May 2016 in countries where IPV introduction will be delayed or regular supply disrupted.	Apr 2016	Ongoing	The topic was discussed at the SAGE Polio WG in August 2016. Given uncertainties surrounding the future supply of IPV, recommendation for catch-up vaccination will be discussed in future WG meetings.
Polio	SAGE encouraged further engagement of WHO regional offices in regard to the polio legacy planning to ensure adequate technical support to countries.	Oct 2015	Ongoing	A Legacy Working Group has been established by the AFRO Regional Director. Planning guidance is now available for countries and the GPEI Transition Management Group (previously Legacy Management Group), which includes representations from EPI and Gavi, among others, is actively engaged in supporting the planning process. Funding has been made available by the GPEI to secure Technical Assistance to 14 countries for planning purposes. There is a joint WHO-UNICEF workplan for supporting the countries of Africa, and a separate workplan for the countries of Asia.
Polio	SAGE requested its Polio Working Group to provide urgent guidance on optimal management of IPV supply and mitigation of other risks in case the IPV supply is further reduced.	Oct 2015	Ongoing	IPV supply situation is being closely monitored. SAGE WG and SAGE issued a statement in March and made recommendations in April SAGE meeting regarding IPV supply. This issue was further reviewed in the SAGE Polio WG meeting in August 2016. Update from the meeting, including discussion with vaccine producers, will be provided in Oct SAGE meeting.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Polio	The documentation for 'legacy planning' should include contributions from communities and front-line health workers on their experiences with the polio programme, what it has meant for them and how lessons learnt could further improve the routine vaccine and health programme.	Apr 2013	Ongoing	Capturing this information is integrated into the country-level transition planning guidelines, and the work of Transition Management Group of the Global Polio Eradication Initiative is emphasising the importance of this.
Polio	SAGE advised GPEI to accelerate implementation of the WHO Global Action Plan for containment (GAPII) including: a) all countries completing phase I; b) regional focal points closely monitoring country activities and ensuring each country completes its inventories of facilities that hold or handle polioviruses, and destroys or commits to destroying WPV2 by end 2015 and any other type 2 containing materials including Sabin poliovirus by July 2016.	Oct 2015	Ongoing	As of 3 August 2016, 204 countries and territories have completed the first part of Phase I, with 1 Member State having yet to respond and 14 Member States yet to complete their reports on the destruction or planned retention of WPV2 or VDPV2 materials. Reports on the destruction or planned retention of all Sabin type 2 poliovirus materials are beginning to be collected in all Regions, as the deadline for completion of the second part of Phase I was set at 31 July 2016, 3 months after the switch. However, guidance on 'Assignment of samples to high, moderate or negligible risk categories of being potentially contaminated with PV2 and recommended conditions for their handling and storage' is still being developed. It is only based on this guidance that countries will be able to complete Phase I, so it is tacitly understood that completion of Phase I will be delayed.
Polio	SAGE advised GPEI to develop a targeted advocacy and communication plan to engage key countries and stakeholders to ensure completion of phase I and implementation of phase II, including establishment of national containment authority and national regulation for containment of poliovirus in designated essential poliovirus facilities.	Oct 2015	Ongoing	A communications plan and a new web page for poliovirus containment have been developed. A map showing global progress on completion of phase I of GAPII is posted every week. The map also identifies countries that have designated poliovirus-essential facilities and have nominated national authorities for containment that will certify facilities against GAPII. In addition, the much awaited new guidance 'GAPII Containment Certification Scheme' is undergoing internal clearance for publication and will be made available shortly for NACs and PEFs to start containment certification activities under the global oversight of the Global Commission for the Certification of Poliomyelitis Eradication.

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Polio	SAGE advised the GPEI to ensure a full outbreak response to interrupt the cVDPV2 outbreak in Guinea and in South Sudan within 120 days of outbreak confirmation.	Oct 2015	Ongoing	<p>1. Guinea: Seven cVDPV2 cases have been reported in Guinea from September through December 2015, all under the age of 5 years. These are genetically linked to a case from August 2014 for which response was hampered due to the Ebola outbreak. Seven SIAs were carried out using tOPV between September 2015 through April 2016. The country completed the switch to bOPV on 30 April 2016. The first outbreak response assessment took place on 29 February 2016, and another is currently underway (starting August 2016).</p> <p>Main recommendations are: improving commitment of national authorities; strengthening immunity in the population through routine immunization and SIAs, including reinforcing communication and social mobilization; improving sensitivity of surveillance and optimizing management of international consultants.</p> <p>Main risk and challenges are: inability to ensure interruption in transmission due to surveillance gaps; undetected low level circulation possible (consultants now focused on two regions, thus surveillance efforts in the rest remains understaffed. Medium to high risk of exporting polio virus to neighbouring countries, especially Liberia and Sierra Leone through migrant workers, population movement. Insufficient ownership of the PFA database by the EPI coordination); low involvement of national actors at the provincial and district level; repeated mistakes in investigation sheets, irregular follow-up meetings, large number of AFP samples (n=229) pending in Dakar lab database (overflow from increased sampling will be sent to other approved labs to accelerate pace of testing).</p> <p>Although there is an improvement in SIAs, micro-plans for SIAs should be updated to address shortfalls and lessons learned. Need to work on the reasons for missed children. National public health emergency not yet declared.</p> <p>Funding shortfall: half of international consultant contracts will end by the end of September and insufficient funds for contracts; Insufficient funds for active case search in June - July in Kankan and Faranah).</p> <p>2. South Sudan: South Sudan reported 2 cases in Rubkona County, Unity State with the latest onset on 12 September 2014. In 2015 one aVDPV2 case was identified in Mayom County, Unity State (adjacent to Rubkona County) with an onset of 19 April 2015. It was 14 nucleotides different from Sabin 2 but not related to the 2014 outbreak nor any other strains. Switch was confirmed by the country on 1 May 2016. The country was supported with 25 international STOP team members as well as 8 international and 38 national consultants from WHO, UNICEF and BMGF, deployed to support outbreak response. In response to the outbreak, a total of 10 vaccination campaigns (4 NIDs, 2 sNIDs, 3 SIADs) were carried out in the counties of three conflict affected states (Jonglei, Unity, and Upper Nile). The assessment team recognized that there has been significant improvement in the quality of surveillance, the quality of SIAs, and application of communication strategies, particularly in conflict affected states. The team concluded that given the improvements in surveillance (NPAFP rates greater than 3.8 nationally and in conflict affected states), and the non-detection of poliovirus for more than 13 months, that it was unlikely that the surveillance system had failed to pick up persistent transmission. Nonetheless, sub-optimal specimen adequacy and silent counties, as well as pockets of under-immunized children especially in conflict affected ones. Outbreak Response Assessment recommendations included strengthening of coordination between MoH and partner agencies, conducting bottom-up micro planning before the next SIA, improving IPV coverage, active case search and specimen transport, and accelerating rollout of community based surveillance in conflict affected states.</p>

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Polio	Sufficient capacity should be established at the global level to provide technical and programmatic support to countries to plan and implement all activities associated with type 2 oral polio vaccine (OPV2) withdrawal and introduction of inactivated polio vaccine (IPV).	Apr 2013	Completed	<p>The Immunization Systems management group, co-chaired by WHO and UNICEF, has been established to coordinate efforts towards the activities relating to OPV2 (type 2 component of oral polio vaccine) withdrawal and IPV (inactivated polio vaccine) introduction. The multi-partner group has been operating since mid-April 2013 in five areas of work: Regulatory, vaccine implementation, communication, financing and routine immunization strengthening.</p> <p>Since April 2013, significant time was dedicated to the Immunization Systems Management Group by the staff of the six agencies: Center for Disease Control and Prevention (CDC), WHO, UNICEF, Bill and Melinda Gates Foundation (BMGF), Rotary and Gavi.</p> <p>WHO/EPI (Expanded Programme on Immunization) has filled additional 3 professional staff positions at HQ to support this effort. UNICEF HQ has filled two additional HQ positions. Significant numbers of staff and consultants have also been deployed at Regional levels of both organizations, and funding has been sent to all regional offices.</p> <p>All of the expected Gavi-eligible countries (71) have applied and been approved for IPV introduction support. For non-Gavi countries, a financing mechanism has been rolled out to support 16 countries in Tier 2 and Tier 3 or LMIC (low and middle income countries) which are non-Gavi eligible. This mechanism will enable partners to support some countries that need vaccine introduction grants and/or time limited procurement of IPV. In December 2014 the above financing mechanism was extended to another 9 countries from the American (AM) and Western Pacific (WP) regions to help them initiate the procurement of IPV.</p> <p>To date, 92 countries introduced IPV since January 2013, including all 17 tier 1 countries and 14/19 tier 2 countries. Due to the IPV supply shortage, 20 low-risk countries and one self-procuring country (Indonesia) will introduce IPV after the switch.</p> <p>The switch was successfully carried out in April 2016, sufficient capacity was established at the global level to provide technical and programmatic support to countries to plan and implement all activities associated with OPV2 withdrawal.</p>
Polio eradication	SAGE requested the polio Working Group to continue monitoring progress towards cVDPV2 elimination and ensuring that remaining challenges are addressed including contingencies for vaccine supplies (IPV, bOPV and tOPV), registration of bOPV for routine use, surveillance sensitivity, and reaching inaccessible children.	Apr 2015	Ongoing	<p>The Polio Working Group reported to SAGE in October 2015 and SAGE reconfirmed April 2016 as the definite date for OPV2 withdrawal. The OPV2 withdrawal was implemented in late April to early May 2016.</p>
Regulatory	SAGE recommended that the further development of the Emergency Use Assessment and Listing procedure being developed by WHO, which would allow use of a vaccine in the context of a Public Health Emergency of International Concern, be done in close consultation with relevant regulatory authorities, including those of the affected countries.	Apr 2015	Ongoing	<p>A document entitled, "Vaccine evaluation in public health emergencies – review of regulatory pathways in selected countries" was prepared and presented to SAGE WG on Ebola vaccines in August 2015. In October 2015, the document was submitted to the Expert Committee on Biological Standardization (ECBS) for review and advice. The Committee considered that a guidance document might be of value to National Regulatory Authorities (NRAs) and other public health organizations. However, it also recognized the complexity of emergency situations, each of which is essentially unique, and that decisions ultimately rest on a benefit/risk assessment. The ECBS agreed to review the document's progress in 2016.</p>
Reports from other advisory committees	SAGE recommended appointment of appropriate programmatic and implementation expertise to IVIR-AC membership including representation of experts from low and middle-income countries.	Nov 2011	Ongoing	<p>Since 2013, Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) includes two programmatic and implementation research members from the African Region (AFR) and the South East Asian Region (SEAR). Since 2014, IVIR-AC includes a mathematical modeler/economist from SEAR and a medical anthropologist from AFR. Currently 2 seats are vacant for health economists with experience in vaccine implementation research. Recruitment of new members is ongoing. There was a call for new members in 2015. Three potential candidates were selected to attend the June 2015 meeting. The mathematical modeler was selected to become a member but the two health economists were not selected as they did not meet the expectations. A new call for Committee Members will be issued in Q3-Q4/2016.</p>

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Reports from other advisory committees on immunization	WHO and NIBSC should develop with other stakeholders, a business plan to assure long-term security of the development of WHO reference preparations as a global public health resource and additional efforts should be undertaken to disseminate outcomes of the committees deliberations and to explain the relevance of its work to the broader immunization community.	Nov 2006	Pending	A comprehensive review of the work of the Expert Committee on Biological Standardization (ECBS) is ongoing. The review will include (but not be restricted to) consideration of communication of ECBS outcomes. Discussion on a paper on the process of the review was initiated by ECBS during its October 2014 meeting. However, biotherapeutic biological drugs were identified as first priority.
RSV	SAGE asked for preparations to be made to support global policy-making for respiratory syncytial virus (RSV) maternal immunization as well as passive immunization with long-acting mAb. SAGE emphasized the need to link maternal immunization platform strengthening with influenza, tetanus and pertussis vaccines along with preparations for potential country introductions of RSV vaccine.	Apr 2016	Ongoing	Further discussions have been held with the PQ team with regard to prequalification processes for both RSV vaccines and mAbs. The ECBS Guidelines for RSV vaccines are planned for development and possible adoption at ECBS 2018, as these are a prerequisite for consideration for PQ. The Essential Medicines department is considering an approach to PQ of mAbs. Intensive discussions continue about the most appropriate way to prepare for policy-making in LMICs, without any results yet available for efficacy trials in these settings. A Phase 3 trial of the Novavax RSV F Vaccine in 11,856 older adults (60 years of age and older, enrolled in the USA), did not meet the pre-specified primary or the secondary efficacy objectives, and did not demonstrate vaccine efficacy. This information is from a press release dated 15 September 2016, and a full review of the data will be necessary to understand what may underlie them. Clearly efficacy may differ between elderly and healthy pregnant women target groups. The Novavax Phase 3 trial in late 2nd/early 3rd trimester pregnant women continues with endpoints accruing in neonates and young infants. The RSV vaccine pipeline remains very robust and can be accessed at the IVR Vaccine Pipeline Tracker: http://who.int/immunization/research/clinicaltrials_newvaccinepipeline/en/ (open the page then navigate to the RSV tab of the spreadsheet)
Second year of life (2YL)	SAGE requested that the final guidance for national programmes to establish routine healthy child visits during the second year of life (2YL) be reviewed by the Immunization Practices Advisory Group and then sent to SAGE for endorsement.	Apr 2016	Ongoing	The 2YL guidance is being prepared by a consultant and will then be used to implement in 4 countries in 2017. Following this, the guidance will be presented to IPAC and SAGE for endorsement (probably by early 2018).
Smallpox vaccines	SAGE recommended that WHO initiate discussions with countries in possession of smallpox vaccine to establish mechanisms for replenishment of the WHO stockpile in case of need.	Nov 2013	Ongoing	Discussion with the French Government for the donation of 5 million doses and Japanese Gov for 10,000 doses are still ongoing. WHO is working on smallpox vaccine prequalification for the emergency stockpile. A WHO meeting took place in Geneva 7-8 September 2015 to discuss with the National Regulatory Authorities and vaccine manufacturers what would be the minimum criteria to pre-qualify smallpox vaccines in case of re-emergence of variola virus. The report is envisaged to be published in Q4 2016.
Strengthening of NITAGs	SAGE requested a regular update on the number of established National Immunization Technical Advisory Groups (NITAGs).	Apr 2016	Ongoing	This information is collected via the WHO/UNICEF joint reporting form and analyzed every year. The figures are included in the GVAP secretariat report, which is made available to the SAGE DoV working group and then to SAGE. Although some data verification is still pending, in 2015 127 countries reported the existence of a NITAG and 77 countries the existence of a NITAG that meets all 6 basic process indicators included in the JRF and used as part of the GVAP indicator. These figures can also be included in the global report on a yearly basis. A specific NITAG session is planned for the April 2017 SAGE meeting.
Supply shortages	SAGE proposed as immediate action to communicate effectively to countries on causes of shortages and current mitigation and long term activities.	Apr 2016	Ongoing	Shortage discussion was integrated into the GVAP secretariat report and regular quarterly calls with regions. More actions have been conducted regarding specific vaccines, such as YF or IPV, for which clear impacts of the current shortages have been identified and are being addressed with both short and long term strategies. For other vaccines, actions have been limited by the lack of resources, concentrating instead on assessing the feasibility of creating a supply exchange forum.

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Supply shortages	SAGE recommended that WHO could play a key role in setting up an "Exchange Forum", helping to collect demand information from all Member States and to enhance dialogue between countries' demand (including anticipation of schedule evolution and new introductions) and manufacturers' supply availability and risks.	Apr 2016	Ongoing	Concerns about ongoing shortages of vaccines persist. Internal WHO discussions and discussions with partners are in progress, in light of the SAGE session on vaccine shortages held in April 2016 and of resolution 69.25 on "Addressing the global shortage of medicines and vaccines." WHO IVB Department, in collaboration with EMP and with support from Linksbribe consulting, is leading a project to set up an "Exchange Forum" to enhance dialogue between countries and manufacturers on demand predictability, supply availability and potential threats to vaccine supply, particularly for vaccines and countries not supported by UNICEF Supply Division or Gavi. In order to make sure that the Exchange Forum is built on existing data, knowledge and processes, WHO secretariat (IVB, in coordination with EMP) is following a two-phase approach. Phase 1 will focus on mapping existing information and highlighting gaps. Based on results from Phase 1, a Phase 2 may be launched to develop a platform or exchange forum to make sure that all available and appropriate information identified in Phase 1 is shared with countries, manufacturers and partners.
Surveillance	SAGE endorsed the recommendations of the ad hoc TAG for improving the quality of the IB-VPD surveillance network and urged that the objectives of this network be more clearly defined, that collaboration with other surveillance systems and laboratory networks (i.e. the polio/measles laboratory networks) be continued, and that, where feasible, activities be linked with other programmes enhancing country capacity, including implementation of the International Health Regulations. SAGE urged greater attention to integration of data systems, which would facilitate real-time analysis and performance monitoring. SAGE also noted the opportunities for integration by building upon the enhanced capacity developed by these networks to conduct surveillance for other diseases using a similar case-definition and personnel trained in applying and adhering to rigorous surveillance protocols. Both networks should continue to share experiences with the polio surveillance network. Integration efforts must be strategically designed in ways that are logical and synergistic.	Nov 2013	Ongoing	During 2013, a global strategic review was conducted of the invasive bacterial vaccine preventable diseases (IB-VPD) and rotavirus sentinel hospital surveillance networks. During that meeting, 50 recommendations were made to advance the status of both networks. During 2014 and 2015, significant progress was made to further improve the IB-VPD and rotavirus sentinel hospital surveillance networks and additional recommendations made. By 2016, we have made significant progress toward strengthening the Networks and meeting those goals. In 2015, the Global Rotavirus Surveillance Network comprised 114 sentinel surveillance sites in 53 countries and the Global IB-VPD Surveillance Network comprised 114 sentinel sites in 52 countries. Data management processes continue to be improved toward a more systematic approach in reporting, cleaning, analysing and interpreting data. The reference laboratories are appropriately supporting sites and network laboratory performance has been successfully monitored by the global external quality assessment program as well as quality control programmes. Sentinel site and laboratory assessments are ongoing at priority sites. The most recent data available is from 2015, and it reflects the strength of the data and the network. Network data has contributed to vaccine introduction decisions, such as choice of Pneumococcal Conjugate Vaccine (PCV) formulation, and the surveillance networks have been used as platforms for vaccine impact evaluations, particularly for Rotavirus Vaccines (RV). Moving forward, the rapid introduction of PCV and RV by Member States now requires the surveillance networks to focus on improving baseline data for sites in non-vaccine using Member States and to ensure consistent surveillance practices for sites that meet inclusion criteria in vaccine-using Member States. A web-based data management tool is being rolled out in one Region (PAHO) and has great potential to improve data quality and sharing across the Network. Some new activities involve testing for other pathogens and integrating with other VPD surveillance platforms. Specifically, a pilot to include typhoid surveillance as part of IB-VPD surveillance has started in 2 sites in Asia and 2 in Africa. We are discussing how to better integrate IB-VPD meningitis surveillance with existing meningococcal meningitis surveillance systems. We conducted a survey of existing capacity to explore how to use the rotavirus surveillance network to monitor norovirus, and a network study will be launched in late 2016 using the TAC technology to test for other enteric pathogens including ETEC and Shigella in specimens collected as part of the network. We are planning a meeting to evaluate the cost of surveillance to help countries and funders develop sustainable surveillance plans, including other VPDs such as measles. We also continue to support sites where PCV and/or RV vaccine impact evaluations may be feasible due to sufficient pre- and post-vaccine introduction data, including using secondary data sources such as hospital administrative data. We have an ongoing evaluation of what sites to include in the Network, how to incorporate countries conducting surveillance outside of the Network, and how to make surveillance sustainable in the long term.

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Sustainable Development Goals	Approval of a vaccination coverage indicator under the child mortality target of the Sustainable Development Goals (SDGs) has not yet been obtained. SAGE urged WHO and countries to request an aspirational immunization indicator under the SDGs.	Apr 2016	Ongoing	Several immunization partners (Gavi, Unicef, BMGF, US-CDC, WHO, Center for Vaccine Ethics and Policy NYU) have worked together to explore possible indicators to be added to the SDGs monitoring framework in addition to currently included ones (Target 3.8.1 UHC coverage composite indicator, and the Hepatitis B control strategy, three doses of Hep B vaccine). It was agreed to propose GVAP G2 Indicator Coverage for all vaccines in national schedule to be included for SDGs sustainability and access to health and essential medicines & vaccines goal (3.b).1. The choice of this indicator has been validated by the SAGE DoV WG. The proposed indicator has been submitted to IAEG-SDGs secretariat the 24th June 2016. We are waiting now to hear back from them.
Tuberculosis vaccines	SAGE endorsed the establishment of a WHO TB vaccine technical expert group with representation from SAGE. An annual written report on TB vaccine developments should be provided to SAGE. SAGE would be provided with two-page summaries of progress every year. TB would only be included on the agenda of SAGE when there is a meaningful development of decision from SAGE required.	Nov 2011	Ongoing	Progress in TB vaccine development was reviewed by PDVAC in June 2016. Since the adolescent/adult population carry the heaviest disease burden, there is consensus within the TB vaccine community that prioritizing this target population will have the highest and most immediate public health impact from reduction in transmission. In addition, key data will emerge from separate clinical studies with 2 TB vaccine candidates (VPM1002 and M.Vaccae) during in 2016. M.vaccae is a heat killed homogenized lysate developed by Anhui Zhifei Longcom, China. It is undergoing Phase III testing for prevention of pulmonary TB among adults with latent infection in China. VPM 1002 is a recombinant BCG, originally developed by the Max Planck Institute; now licensed to the Serum Institute of India (SI) and being developed with Vakzine Projekt Management (VPM), Hannover, Germany. It is currently in Phase II trial vs. BCG in HIV+ and HIV- infants <12 days old in South Africa. Interim data assessment is anticipated in 2016, and may also be assessed in a Phase III prevention of recurrence study in adults in India. H4/IC31 is an adjuvanted recombinant protein under development by Sanofi Pasteur, SSI and Aeras, currently in a Phase II prevention of infection study in adolescents (Phase II) with data expected in 2017. GSK also have a candidate undergoing Phase IIb evaluation in TB exposed, HIV negative adults in South Africa, with results expected in 2018. Considering the time frame to phase III studies and licensure, PDVAC recommended that WHO derive guidance on preferred product characteristics for TB vaccines targeted to adults and adolescents. IVB is actively seeking funding for the resources to undertake this over the next 2 years.
Typhoid	Establish a SAGE working group on typhoid conjugate vaccines in 2016 to prepare for a SAGE review of the evidence in 2017.	Oct 2015	Ongoing	The SAGE Working Group on Typhoid Vaccines was established in March 2016 and has initiated the evidence review process. The Working Group will review updated evidence to support the use of typhoid vaccines overall with a focus on typhoid conjugate vaccines. A SAGE review is tentatively scheduled for Oct 2017.
Un/under-immunized children	SAGE requested that WHO quickly roll out tools so that other countries can address low coverage of vaccination.	Nov 2010	Ongoing	The in-depth tool, "A Guide to Tailoring Immunization Programmes (TIP)" has already been developed and used by WHO-EURO (European Regional office). Currently the Univ. of Witwatersrand in South Africa has been contracted to adapt the methodology to developing countries, and less intensive consultant-based inputs. The Health Worker KAP tool has been completed and will be piloted with the assistance of JSI in Kenya. Work is ongoing on the tool to assess "Missed Opportunities". On a broader level, a companion document to the GVAP focusing on Routine Immunization entitled, "Global Routine Immunization Strategies and Practices" (GRISP) is in the final stage of drafting, and has been presented to the SAGE WG on DoV twice. In addition to a comprehensive framework of RI strategies, it highlights nine "transformative investments" to guide global partners and countries in RI strengthening.

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Vaccination during humanitarian emergencies	SAGE emphasized the need to advance work on refining guidance in delivering continuous immunization services during humanitarian conflicts. A session on human emergencies will tentatively be slotted at the April 2016 SAGE meeting.	Oct 2015	Ongoing	<p>A WHO meeting on implementation of vaccination during humanitarian emergency situations was convened in Cairo from 12-14 January 2016. The objectives were to:</p> <ul style="list-style-type: none"> -reflect on the experience of EMR countries in implementing vaccination in humanitarian emergencies and the issues, challenges, best approaches and existing country guidance documents to ensure satisfactory vaccination of the target populations. -reflect on countries experience using vaccination in acute humanitarian emergencies: a framework for decision making. -build on countries experience to initiate development of a draft guidance document on the implementation of vaccination in humanitarian emergency situations. <p>A draft guidance document on implementation issues has been initially produced by EMRO. This document is being adjusted some as a result of limited preliminary peer-review and will soon be distributed for a much broader peer review. 'Vaccination in acute humanitarian emergencies: a framework for decision making' has also been adjusted/updated based on the feedback received during the Cairo meeting and a draft operational manual is being developed. Work is ongoing for the development of web based interactive tools to support its use and facilitate further updating. Attempts will be made to have a proactive dissemination and communication plan to ensure adequate distribution.</p> <p>Finally, although there was no separate specific session during the April 2016 SAGE meeting an update was featured in the IVB Director's global report at this meeting. A meeting was jointly organized with MSF on June 20 to tackle the issue of supply and procurement obstacles in humanitarian emergencies:</p> <ol style="list-style-type: none"> Discuss/map the obstacles to necessary access to affordable vaccines in a timely manner in emergency and humanitarian crisis situations. Discuss proposed solutions for addressing the key barriers to timely provision of affordable vaccines in humanitarian crisis situations. Agree upon a set of priority issues to be addressed by partners with a proposed plan of action/timeframe for follow up. <p>A follow-up meeting will take place on 10-11 October to develop consensus on the various guidance and priorities mentioned above and discuss how to best communicate and advocate for their implementation.</p>
Vaccination during humanitarian emergencies	SAGE also suggested that the framework approach to vaccine decision-making could be considered for other health interventions in emergencies.	Apr 2012	Ongoing	<p>A discussion was held at the MICs Task Force meeting held in February 2015 on the possibilities of having an emergency fund for vaccines in disaster situations. The discussion resulted in a mapping of emergency funds available and gaps, which was presented in the April SAGE meeting in 2015. No further updates have resulted from this discussion.</p> <p>The Emergency Risk Management and Humanitarian Response (ERM) Department is currently undergoing a reform process. Once the process is finalized we will have a clearer indication of our engagement in and collaboration with this area of work.</p>
Vaccine coverage	WHO to identify appropriate methods and develop guidelines for collecting, analysing, and interpreting biomarkers for validating coverage.	Nov 2011	Ongoing	<p>Currently, WHO is developing global guidelines on conducting serosurvey studies on measles and rubella and primarily to be applicable in a pre- and post-SIA (supplementary immunisation activity) setting. An expert working group has been assembled and based on the expertise in the various fields of each of the members, needed to conduct such studies, including statisticians, epidemiologists, laboratory experts, and program experts, given sub-tasks in developing parts of these guidelines that pertain to their respective expertise.</p> <p>A working draft has been circulated for comments and was finished by the end of 2015. It was tested subsequently in pilot studies in two different settings, pre- and post-campaign, for its applicability. A pilot study is taking place in Mongolia in 2016. Based on the outcome, the working draft guidelines will be corrected where needed and finalised. The final document is planned to be ready by end of 2016 and to be rolled out as a tool to evaluate the immune status of the target or targeted population.</p>

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Vaccine coverage	SAGE recommended that WHO support new research for biological specimen collection including rapid on-site diagnostics that could improve coverage and susceptibility estimates. Improved serological surveillance techniques could be integrated with existing population-based surveys such as DHS or MICS. These research topics should be included on the QUIVER (now IVIR-AC) agenda.	Nov 2011	Ongoing	Bill & Melinda Gates Foundation is now accepting Letters of Inquiry for the development of an easy-to-use tool that rapidly assesses the immune status of children against select vaccine-preventable diseases. Inquiries focusing on prototype development and detailed plans for future commercialization possibilities are welcomed.
Vaccine coverage	SAGE recommended that WHO explore alternative survey methods to improve the precision, reduce the cost and improve the usefulness of survey results to national and local immunization programmes.	Nov 2011	Ongoing	<p>To improve the precision and usefulness of survey results and to reduce the cost of surveys, the Strategic Information Group (SIG) proposes to explore:</p> <ol style="list-style-type: none"> 1) recent advances in sampling methodology, 2) new technologies for constructing sampling frames, supervision of field work, data collection, and analysis, and 3) alternative content, collection, analysis, presentation and linkages with other data sources. <p>An explicit description of precision, usefulness and cost of various trade-offs between alternative methods will constitute part of the exploration.</p> <p>An initial meeting was convened of the Department of Immunization Vaccines and Biologicals (IVB) Informal Advisor Group on Monitoring Immunization Programme Performance through Household and Community Surveys. First meeting addressed the need to modify Demographic and Health Surveys (DHS) implemented by ICF International; and the UNICEF Multiple Indicator Cluster Surveys and the WHO Immunization Cluster Survey to accommodate changes in immunization system strategies.</p> <p>On 17-18 September 2012, a meeting was held with representatives of ICF and UNICEF to discuss modifications to their standard recommendations on data collection, analysis and presentation of immunization coverage data. WHO and UNICEF provided written recommendation to these agencies.</p> <p>An informal working group has been created to review and revise WHO guidance on measuring immunization coverage through household and community surveys.</p> <p>The working group met in July 2013 to agree on the scope of work, to identify initial products, and establish a plan of document production, review, pilot testing, and clearance. Draft guideline was circulated to external reviews. Protocol for pilot testing was developed and pilot testing is currently undergoing in Bangladesh.</p> <p>The proposed methods were reviewed in September by Immunization and Vaccines Related Implementation Research (IVIR) Advisory Committee. The methodology is currently tested in Burkina Faso and in Lao PDR. The working draft of the manual has been distributed and posted on the departmental website: (http://www.who.int/entity/immunization/monitoring_surveillance/Vaccination_coverage_cluster_survey.pdf?ua=1).</p> <p>A briefing workshop on the methodology for regional focal points and consultants has been conducted in December 2015.</p>
Vaccine delivery research	SAGE requested that IVIR-AC explore research studies and methods including behavioural science studies for ranking reasons behind lack of vaccine delivery and other 'barriers to access'.	Oct 2015	Ongoing	IVIR-AC reviewed methods, and encourages studies on vaccine delivery costing and financing (HPV, influenza and OCV) and vaccine uptake/hesitancy.
Vaccine Hesitancy	SAGE encourages validation of the developed compendium of survey questions on vaccine hesitancy, which have been assessed and validated only in some high-income countries or not at all.	Oct 2014	Ongoing	Discussions with various stakeholders are ongoing (Centre for Disease Control CDC, WHO EURO, Middle Income Countries MIC task force) on the ways forward to identify partners to take on the validation of the survey questions. The MIC task force framework was presented to SAGE during the April 2014 meeting, which highlighted the importance to advance this initiative. Currently, how to secure funding from donors in support of the listed activities and advance validation of the questions in LMIC settings is being explored. The survey questions have been translated in Arab and French and are available on the WHO hesitancy website: http://www.who.int/immunization/programmes_systems/vaccine_hesitancy/en/

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Vaccine Hesitancy	SAGE acknowledged the necessity to develop core capacities at headquarters and regional level for gaining behavioural insights that can be applied in an integrated fashion for prevention of many communicable and non-communicable diseases, as well as vaccine hesitancy. This will require the involvement of sociologists, psychologists, anthropologists, experts in social marketing, communication experts, and specific disease and vaccine experts.	Oct 2014	Ongoing	Discussions are ongoing within WHO and UNICEF as well as with partners on how to collectively establish core capacities in order to support and provide technical assistance to countries. For this, discussions were initiated on how to advance the establishment of a network of expertise/excellence and collaborating centres by capitalizing on currently ongoing initiatives and activities which have been established and are conducted by WHO (HQ and Regions), partners and stakeholders in the field of vaccine hesitancy. Resources to support related activities are currently being established at HQ and in EURO. A package listing resources from a number of support centers which could assist countries and regions has been prepared and was circulated to regions in December 2015. Sessions and discussions on vaccine hesitancy are held in the context of immunization managers meetings.
Vaccine Hesitancy	SAGE underlined the importance of distributing the matrix of determinants, the definition of hesitancy and the other deliverables to countries and partners.	Oct 2014	Ongoing	Discussions and presentations were held in the context of the immunization managers' meeting in the Eastern Mediterranean Region (EMR) and the African Region (AFR) Task force on immunization (TFI) meetings in 2014 and 2015. A Special Issue on Vaccine Hesitancy has been published in August 2015 in the journal Vaccine with a series of 10 full papers plus one editorial. In conjunction, a WHO press briefing was held on 18 August 2015 to emphasize WHO initiatives addressing vaccine hesitancy. This generated much positive media coverage. A compilation of centers to assist countries in addressing vaccine hesitancy has been finalized and sent to WHO regions to disseminate to countries. A manuscript has been submitted which outlines the results of the 2015 JRF indicators on vaccine hesitancy. The manuscript contains the matrix of determinants and the definition of vaccine hesitancy.
Vaccine safety	SAGE highlighted the urgent need for a safety review of other important vaccines that could be used during pregnancy.	Nov 2012	Completed	A sub-group of the Global Advisory Committee on Vaccine Safety (GACVS) has been launched to address vaccine safety during pregnancy. A finalized version of the GACVS report on safety of immunization during pregnancy has been made available to SAGE in November 2013 and is now available on the Global Vaccine Safety (GVS) website. A new work track was started with WHO Initiative for Vaccine Research (IVR) in order to harmonize safety monitoring during pregnancy clinical trials. WHO is a contributor to the Gates funded Global alignment of immunization safety assessment in pregnancy project that should run until the end of 2016. WHO is also advising another Gates funded project with Seattle Children's hospital on maternal immunization pharmacovigilance in low- and middle-income countries.
Vaccine Supply	SAGE requested WHO to produce a report on the security of the supply of affordable vaccines and encouraged donors to invest in the development of new vaccine technologies that facilitate the delivery of effective, affordable vaccines to populations most at risk.	Nov 2012	Ongoing	Also see item 331. Concerns about ongoing shortages of vaccines persist. Internal WHO discussions and discussions with partners are in progress, in light of the SAGE session on vaccine shortages held in April 2016 and of resolution 69.25 on "Addressing the global shortage of medicines and vaccines". WHO secretariat (EP) is now working to develop an approach to improve the availability of information regarding supply and demand as requested by member states, the industry, and identified as a contributing factor to shortages. This may lead to the development of an exchange platform to facilitate communication between supply and demand.
Yellow Fever	SAGE requested WHO to revisit the IHR provisions relating to the period of validity for international certificates for vaccination against yellow fever (YF).	Apr 2013	Closed	The WHO World Health Assembly in May 2014 adopted an amendment to Annex 7 of the International Health Regulations (2005) (IHR), which stipulates that the period of protection afforded by yellow fever vaccination, and the term of validity of the certificate will change from 10 years to the duration of the life of the person vaccinated. The amendment entered into force and became legally binding upon all IHR States Parties on 11 July 2016. There were no legal rejections or reservations expressed by countries. For countries with risk of yellow fever transmission and countries requiring yellow fever vaccination (see http://www.who.int/ith/2016-ith-annex1.pdf?ua=1).

WHO/AFRO
REGIONAL IMMUNIZATION
TECHNICAL ADVISORY GROUP MEETING

FINAL REPORT

BRAZZAVILLE, CONGO
05 - 08 JULY 2016

TABLE OF CONTENTS

TABLE OF CONTENTS.....	I
EXECUTIVE SUMMARY	II
ACRONYMS.....	V
1.0 BACKGROUND.....	1
2.0 INDUCTION BRIEFING.....	2
2.1 OPENING	2
2.2 OVERVIEW OF WHO/AFRO, SAGE & NITAG.....	3
2.2.1 <i>Introduction to WHO/AFRO; its structure, governing bodies; relationship with countries and partners; funding sources.....</i>	3
2.2.2 <i>SAGE and its link with RITAG</i>	3
2.2.3 <i>Role of NITAGs in supporting national immunization programme</i>	4
2.3 BRIEFING ON WHO/AFRO IMMUNIZATION PRIORITY AREAS OF WORK	5
2.3.1 <i>Regional Strategic Plan for Immunization 2014-2020</i>	5
2.3.2 <i>RITAG in the Era of Decade of Vaccines</i>	5
2.4 FUNCTIONING OF RITAG	6
2.4.1 <i>RITAG Future Working Arrangements & Modalities including RITAG Working Groups</i>	6
3.0 RITAG MEETING	8
3.1 OPENING	8
3.2 TECHNICAL SESSION.....	9
3.2.1 <i>Immunization Overview</i>	9
3.2.2 <i>Yellow Fever and Meningitis.....</i>	12
3.2.3 <i>Vaccine Regulation and Universal Immunization Coverage</i>	18
WRAP UP AND CLOSURE.....	24

EXECUTIVE SUMMARY

The newly constituted Regional Immunization Technical Advisory Group (RITAG) met in Brazzaville, from 5th to 8th July 2016. The meeting was officially opened by Dr Joseph Cabore, Director of Programmes and Management (DPM), on behalf of the Regional Director, Dr Matshidiso Moeti. Present during the opening were Cluster Directors and staff of the WHO from the RO, ISTs and HQ.

The primary goals of the meeting were to brief the new RITAG members on the regional priorities for immunization and to seek their advice on current specific challenges. Some of the current priority areas in immunization were discussed in sessions of the meeting after the briefing sessions. In these sessions, the progress made was summarized, challenges highlighted and the RITAG members given the opportunity to discuss and to provide advice. At the end, a number of key recommendations were made.

RITAG Recommendations:

☐ **Immunization coverage and equity**

- Countries, especially those reporting high immunization coverage, should triangulate available data (including sub-national surveys, sero-surveys, and surveillance data) to improve the accuracy of population immunity estimates.
- WHO AFRO to expand research agenda to include the development of new diagnostic tools, mapping, population denominator estimates, and innovative vaccine delivery strategies, and that AFRO move as quickly as possible to implement cost-effective strategies found to strengthen immunization programmes.
- WHO AFRO to support countries to implement activities to address gaps emanating from the findings of the BMGF and Gavi on vaccine stockpiles as soon as available. AFRO should work with partners to ensure that adequate, sustainable funds are available for sufficient vaccine stockpiles, and that timely and dependable deployment mechanisms are identified and implemented.

☐ **Polio eradication initiative**

- In the context of decreased polio funds, a detailed investment case is developed which identifies the resources needed to:
 - a. Maintain essential polio programme functions to ensure that the polio-free status remains.
 - b. Maintain essential routine (non-polio) immunization programme components (e.g. surveillance [including laboratory networks and information infrastructures], risk mitigation, workforce capacity, safe and effective vaccines, outbreak detection/response).
 - c. Introduce and implement activities required to achieve and maintain GVAP and Regional immunization targets

- WHO/AFRO to work with partners to mobilize additional resources to fill funding gaps, including the development of detailed advocacy plans to increase country ownership and leadership, and monitoring government commitments (% EPI funded by government) made at the Ministerial Conference on Immunization in Africa, February 2016 to increase EPI funding.
- WHO/AFRO to work with countries to intensify surveillance for polioviruses by:
 - a. Completing implementation of the Brazzaville and Lake Chad Basin Initiatives to strengthen surveillance in localized areas with surveillance gaps; and,
 - b. Accelerating expansion of environmental surveillance to additional sites in high risk countries.

☐ **Yellow Fever**

- Steps should be taken
 - Reduce response time between identifying cases and implementation of outbreak response interventions.
 - Maintain high immunization coverage in Routine Immunization during outbreaks
 - Revise Laboratory algorithms to include real time PCR.
 - Promote community engagement in vector control activities using lessons from the PAHO region.
 - Review the efficacy and feasibility of the use of fractional doses in situations where stockpiles of vaccine are low.
 - Address cross-border transmission through implementation of IHR 2005.
 - Provide language relevant technical assistance to Angola from PAHO.
 - Appoint two Yellow Fever Focal Points in AFRO to address surveillance and programming.
- Encourage increased vaccine production capacity and thus improved stockpiling.
- Offer guidance to develop an integrated package addressing mosquito-borne infections (aedes aegypti): immunization, detection/case management and vector control. Relevant in terms of global health security.
- Leverage the available in-country PCR equipment for yellow fever diagnosis by providing training and reagents to countries.

☐ **Meningitis**

- Strategies for control of *streptococcus pneumoniae*
 - Noting the changing epidemiology of *S. pneumoniae* meningitis, and the opinion of the expert group, RITAG requests further information on why the expert group believes this was due to biological evolution and not serotype replacement.
 - Noting these outbreaks, the use of PCV in routine immunization should be re-enforced.
 - Re-enforce early diagnosis and improved case management.

- RITAG notes that the pentavalent vaccine (ACWXY) is being developed by Serum Institute of India, and requests that WHO ensures that advanced forecasting is undertaken to address global needs to ensure that Africa has sufficient and affordable supplies to meet requirements.
- Countries planning to introduce MenA into routine immunization need to consider their country specific epidemiology, age-specific attack rates, projected impact, and programmatic experiences.

□ **Vaccine Regulation**

- Strengthening National Regulatory Agencies (and IRBs) through
 - Joint reviews where multi-country projects are undertaken (e.g. malaria vaccine);
 - Expansion to include all regional bodies such as the East Africa Community, SADC, ECOWAS and OCEAC;
 - Learning from countries in the region with strong NRA capacity; and,
 - Advocacy for adequate funding, communication and support.
- In Implementation Pilots and Phase IV Trials, such as the malaria RTS,S vaccine, document results, develop guidance and share lessons.
- Concerning Emergency Response vaccine trials like for Ebola, monitor the process and share lessons within the region, for use in future outbreaks and emergencies. Document best practices in providing speedy review and approval processes.
- Monitor off-label use of vaccines and provide guidance for appropriate regulatory processes such as fractional doses for yellow fever or changes in target groups.
- Liaise among RITAG and other entities to provide a RITAG perspective as well as foster regional coordination in their activities in strengthening NRAs. These groups include AVAREF, PDVAC, G7 CEPI and disease specific task forces, among others.
- WHO should seek the opinion of RITAG about trials for new vaccines (such as EVD, malaria) and for novel use (YF fractional dose, maternal immunization) that have significance in the African region. Specifically, RITAG requests study plans and regular phase IV reports on RTS,S malaria vaccine, and plans for use of Ebola vaccines in outbreaks.

□ **Universal Health Coverage**

- RITAG was pleased to receive information on UHC, and will consider this in its future programme of work. In particular the RITAG noted the following:
 - The importance of SGDs and the proposed inclusion of immunization targets
 - The essential interface between health and development
 - Health systems strengthening is a long term developmental issue
- Noting the publication experience from Nigeria polio programme and Chad nomadic immunization, RITAG recommends that WHO documents best practices for immunization as a contribution to the attainment of universal coverage.

ACRONYMS

AFRO	African Regional Office	LGA	Local Government Area
AFP	Acute flaccid paralysis	LMIC	Low and middle income countries
ANC	Ante-natal care	LQA	Lot Quality Assurance
ARCI	African Regional Conference on Immunization	MCIA	Ministerial Conference on Immunization in Africa
ARICC	Africa Regional Inter-agency Coordination Committee	MCH	Maternal and Child Health
AVAREF	African Vaccine Regulatory Forum	MCV	Measles-containing vaccine
BMGF	Bill and Melinda Gates Foundation	MCV1	First dose of MCV
bOPV	Bivalent oral polio vaccine	MCV2	Second dose of MCV
CDC	US Centers for Disease Control and Prevention	MOF	Ministry of Finance
cMYP	Comprehensive multiyear plans for immunization	MOH	Ministry of Health
CRS	Congenital rubella syndrome	mOPV	Monovalent oral polio vaccine
CSF	Cerebrospinal fluid	MNT	maternal and neonatal tetanus
CSO	Civil society organisations	MR	Measles-rubella [vaccine]
CTC	Controlled Temperature Chain	MSF	Médecins sans Frontiers
cVDPV	Circulating vaccine-derived poliovirus	NGO	Non-governmental organization
DHF	Dengue Hemorrhagic Fevers	NIDs	National Immunization Days
DHS	Demographic and Health Surveys	NITAG	National Immunization Technical Advisory Group
DOPV	Directly Observed Polio Vaccination	NNT	Neonatal tetanus
DQS	Data quality self-assessment	NRA	National Regulatory Authority
DQWG	Data Quality Working Group	OPV	Oral polio vaccine
DTP	Diphtheria-tetanus-pertussis [vaccine]	PAB	Protection at birth
EPI	Expanded Programme on Immunization	PAHO	Pan American Health Organisation
Gavi	Global Alliance for Vaccines & Immunization	PCR	Polymerase Chain Reaction
GIS	Geographic Information systems	PCV	Pneumococcal conjugate vaccine
GPEI	Global Polio Eradication Initiative	PID	Pneumococcal invasive disease
GPS	Geospatial positioning system (GPS)	RCV	Rubella-containing vaccine
GVAP	Global Vaccine Action Plan	RED	Reaching Every District Approach
HPV	Human Papilloma Virus Vaccine	RITAG	Regional Immunization Technical Advisory Group
HR	High Risk	RV	Rotavirus Vaccine
HSS	Health systems strengthening	SAGE	Strategic Advisory Group of Experts on immunization
ICC	Inter-Agency Coordinating Committee	SIAs	Supplementary immunization activities
IDSR	Integrated Disease Surveillance & Response	tOPV	Trivalent oral polio vaccine
IMCI	Integrated Management of Childhood Illness	TFI	Task force for Immunization
ICC	Inter-Agency Coordinating Committee	TT	Tetanus toxoid
IDSR	Integrated Disease Surveillance & Response	UNICEF	United Nations Children's Fund
IMCI	Integrated Management of Childhood Illness	VAP	Vaccine associated poliomyelitis
JRF	The WHO UNICEF Joint Reporting Form	VCMs	Volunteer community mobilisers
		VHF	Viral Hemorrhagic Fevers
		VPD	Vaccine Preventable Disease
		YF	Yellow Fever
		WHA	World Health Assembly
		WHO	World Health Organization
		WPV	Wild poliovirus

1.0 BACKGROUND

This is the first of two regular meetings of the newly reconstituted Regional Immunization Technical Advisory Group (RITAG) of the WHO African Region in 2016. On assumption of office earlier this year, the Regional Director Dr Matshidiso Moeti defined new strategic priorities in engaging the member states, partners, and stakeholders to re-position the organization to address the health priorities of member states. She identified universal health coverage and equity in access as the flagship of the transformation agenda put in place in the Region.

In the light of the above the Regional Director reconstituted and transformed the former Task Force on Immunization (TFI), the principal advisory group to the WHO Regional Office for Africa (WHO/AFRO) for development of policies related to vaccines and immunization, to a RITAG. Additional experts were brought on to work with some of members of the TFI. New terms of references (ToRs) were developed to guide the functioning and role of the new RITAG.

The RITAG is set up to advise the office of the Regional Director on the adequacy of the regional immunization strategic plan and corresponding priority activities to achieve the goals of the Global Vaccine Action Plan (GVAP), taking into consideration the comparative advantages and respective roles of partner organizations. The RITAG is also expected to monitor progress, major risks/challenges and threats, propose recommendations to address these and to achieve GVAP and other global health targets, including the Sustainable Development Goals (SDG) within the WHO African Region.

Noting that 8 out of the 15 RITAG members are newly appointed, and taking into consideration that the mandate of the RITAG now extends to the control of all vaccine preventable diseases, promoting immunization throughout the life course, in the context of health systems strengthening, an in-depth RITAG members' briefing/meeting was convened at the WHO Regional Office for Africa, Brazzaville, Congo, from 05-08 July 2016. The three-day meeting focused on:

- Briefing RITAG members on the work of WHO in general and its on-going reforms;
- Briefing RITAG member on the transformation agenda of the WHO/AFRO;
- Appraising RITAG members on the WHO's regional priorities in the area of immunization, and programmatic challenges being faced;
- Agreeing upon the modus operandi for RITAG over the coming 3 year period; and
- Eliciting RITAG recommendations on key immunization related challenges and issues faced by the region, namely yellow fever and meningitis, vaccine regulation, and universal immunization coverage, among others.

This report provides a detailed account of the meeting and its key outcomes.

2.0 INDUCTION BRIEFING

2.1 Opening

The meeting was officially opened on behalf of the Regional Director by Joseph Cabore, Director of Programmes and Management (DPM), on Tuesday 5th July, 2016. He thanked the 15 RITAG members for accepting the invitation to serve on the WHO AFRO RITAG and to offer their skills and experience; 8 for an initial period of 3-years and 7 for continuing to serve for a further 3-year period.

He reminded the members about the Terms of Reference of the RITAG. The DPM also made reference to the first-ever Ministerial Conference on Immunization in Africa (MCIA) that took place in Addis Ababa in February 2016. “We now have the opportunity to build upon this momentum to generate lasting impact by ensuring the signed Ministerial Declaration entitled: Universal Immunization Coverage as a Cornerstone for Health and Development in Africa, is effectively implemented”, he stated.

The two reoccurring themes throughout the MCIA were strong political commitment and the active engagement of communities in demanding vaccines and immunization services, both critical to achieving GVAP goals within the African region. He called upon RITAG Members to advise the WHO Regional Office on actions to take to ensure that the momentum from the Ministerial Conference is built upon – an effort that is particularly timely as the world enters the second half of the Decade of Vaccines.

The RITAG Chair, Professor Helen Rees, welcomed both old members of the TFI, now RITAG and the new members. She underlined the unique role WHO plays in public health as an organization with UN mandate to provide global guidance for health and delivery of health services. She indicated that there is a lot of unfinished work with old diseases like rabies, but also new emerging diseases. The committee will have lots of work to help shape the thinking around how vaccines and immunization can be used to tackle these issues. The RITAG Chair reminded members that in their advisory capacity to WHO, RITAG can make a profound difference to achieving the target of full benefits of immunization to all in the African Region.

Okwo-Belle, Director of Immunization, Vaccines and Biologicals, HQ, noted that RITAG will be expected to advise WHO/AFRO on what should be done to support countries as well as advising countries in what they should be doing to move the immunization agenda forward.

On behalf of Felicitas Zawaira, Director Family and Reproduction Health (FRH), Richard Mihigo, Manager, Immunization and Vaccine Development (IVD) programme, WHO/AFRO presented the programme of work (annex 1) for the meeting. He noted that the organization is keen on hearing RITAG’s advice on yellow fever and meningitis outbreak responses among other issues.

2.2 Overview of WHO/AFRO, SAGE & NITAG

2.2.1 Introduction to WHO/AFRO; its structure, governing bodies; relationship with countries and partners; funding sources

Dr Richard Mihigo, IVD, WHO/AFRO

Richard Mihigo took members through the structure of the organization, highlighting its governing bodies and its relationships with countries and partners as well as its funding sources. In doing this, he illustrated the core values of the organization to include equity, social justice, universality and people centeredness. He noted that the landscape has evolved from 1948, when WHO was the only organization charged with the task of ensuring public health, to-date when multiple players are operating in the health sector.

He also addressed:

- 1) The WHO Reforms, highlighting the organization's vision, and its six key programmes of work, the five main areas of WHO managerial reform in pursuit of organizational excellence, as well as the WHO/AFRO's transformation agenda.
- 2) Funding and the budget and the top 20 voluntary contributors to the organization.
- 3) Immunization priorities of the WHO in the African Region.

Comments and Observations

1. WHO AFRO should document the contributions made by member states to immunization both directly to their own programmes and through WHO.
2. The changing landscape with increased involvement of many partners in health should be taken positively. It is the responsibility of RITAG to help WHO strengthen its coherence in a 'chaotic' environment, and distinguish itself as leader in the field.
3. In summary, Chair of RITAG noted that the best solutions are win-wins. She stressed the need to think about how with all these partners, the win-win scenario can be achieved. WHO needs to distinguish its leadership role, and exploit its comparative advantage.

2.2.2 SAGE and its link with RITAG

Jean-Marie Okwo-Bele, IVB, WHO Geneva

He presented the mandate of the Strategic Advisory Group of Experts (SAGE) on Immunization, which is the principal advisory group to WHO for vaccines and immunization. SAGE advises on global policies and strategies, ranging from vaccines and technology, research and development, to delivery of immunization and its linkages with other health interventions as well as makes recommendations on use of vaccines, which drive WHO position papers. He discussed the mode of operation of the SAGE as well as the preparations for SAGE meetings and agenda-setting.

He also addressed/noted that:

- 1) Issues taken into consideration by SAGE include disease epidemiology, clinical characteristics, vaccines and immunization characteristics, and economic considerations. Others include health system opportunities and existence of, and

interaction with other existing interventions and control strategies, as well as social impact/legal considerations/ethical considerations.

- 2) The pathways for WHO recommendation on vaccine use as well as immunization policy advisory framework, among others.
- 3) SAGE meetings are often composed of two categories of agenda items, namely the running items and specific topics. Under the running items, the SAGE considers global reports, reports from Gavi and reports from other advisory committee on immunization. The specific topic items are dictated by the current immunization priorities and realities.

Comments and Observations

1. RITAG can request a topic for inclusion on SAGE agenda e.g., vaccine specific to the region or implementation issues related to vaccine delivery. RITAG input would be useful in helping focus the SAGE agenda.
2. RITAG can adopt and adapt SAGE recommendations for the region.
3. It would be helpful to establish a peer review process with a clear window allowing for feedback on publications prior to them being published.

2.2.3 Role of NITAGs in supporting national immunization programme

Blanche Anya, IVD, AFRO

The presence of a functional independent technical advisory group is one of the indicators of this first strategic objective of the GVAP and RSPI. RSPI has a target of 20 countries with functional National Immunization Technical Advisory Group (NITAG) by 2015; 40 countries by 2017; and, all 47 countries by 2020. However, many countries in the Region are yet to establish NITAGs. Additionally, existing NITAGs do not always fulfil all criteria of functionality.

The role of the NITAG is to provide guidance to policy makers and to make evidence based immunization related policy decisions based on local epidemiology and cost effectiveness. NITAG membership consists of 10-15 independent experts with broad range of disciplinary backgrounds. The advantages of having a NITAG include the provision of timely, evidence-based recommendation on vaccine policy in the country as well as placing global and regional recommendations in the context of the country among others.

As of June 30, 2016, only 18 countries indicated having NITAGs in the AFRO region. The main challenges include low appreciation by countries of the role of NITAGs, including difference with inter-agency coordinating committees (ICC) and working groups. Some useful resources that can be accessed from the NITAG Resource Centre through the link <http://www.nitag-resource.org>

Comments and Observations

1. NITAGs should be locally funded by the government rather than externally if they are going to play a truly independent role in advising the government for services that may be heavily externally funded.
2. Available TORs differentiate NITAGs from ICC; ICCs help countries with implementation, while NITAG provides policy advice.

3. RITAG could propose coordination of meetings so that they can feed into each other from SAGE, RITAG to NITAGs. We should consider rotation of invitations to RITAG for NITAG chairs.
4. Confidentiality clauses should be added to the SOPs of NITAGs, recognizing that meetings of these groups will increasingly become public.

2.3 Briefing on WHO/AFRO Immunization Priority Areas of Work

2.3.1 Regional Strategic Plan for Immunization 2014-2020

Balcha Masresha, WHO/AFRO

He presented the Regional Strategic Plan for Immunization (RSPI) 2014-2020. The development of the RSPI followed a comprehensive consultative process involving countries and partners on the need to develop a regional plan that is aligned to the GVAP, after the 2013 independent evaluation of the Regional Immunization Plan of 2009-2013. The TFI approved the draft RSPI in May 2014, and in November 2014 the Member States of the WHO African Region endorsed the RSPI during the 64th session of the Regional Committee.

The strategy aims to achieve universal immunization coverage within the African Region. The objectives include: to increase vaccination coverage; complete the interruption of poliovirus transmission and ensure virus containment; eliminate measles and advocate for the elimination of rubella and congenital rubella syndrome; as well as attain and maintain elimination/control of other vaccine preventable diseases. The guiding principles include country ownership, partnership and mutual accountability, access to universal health coverage and integration, sustainability, innovation and quality improvements. Clear roles and responsibilities have been defined for all stakeholders including governments, communities, WHO and partners.

2.3.2 RITAG in the Era of Decade of Vaccines

Helen Rees, Chair, RITAG, WHO/AFRO

She recapped the genesis of the decade of vaccines, and noted that all 193 Member States of the World Health Organization approved the need for a global vaccine action plan at the 64th World Health Assembly in May 2011. Our region however still has exceptional unmet needs for vaccines and immunization.

She also noted that:

- 1) The quality of data currently reported was inadequate to reliably monitor progress and make programmatic decisions.
- 2) Polio eradication remains a public health priority.
- 3) We should ensure access to quality vaccines and new technologies to drive progress.

Comments and Observations on Presentations by Dr Masresha and Prof Rees

1. The right to health by all peoples and health as a human right should be referenced.
2. Lessons could be learned from the onchocerciasis programme. Communities should not just be consumers, but be involved in planning and delivering immunization programs.

3. We need to support research and training institutions in the strategic plan. The plan should also address emerging diseases that will need vaccines and immunization.
4. Routine Immunization should continue during emergencies. This should be addressed at the mid-term evaluation next year.
5. The components of the WHO blueprint on R&D should be institutionalized e.g., which pathogens, and design of clinical trials, in advance of epidemics.
6. RITAG can shape the work of GAVI, especially guidance for the region. This has worked well between WHO/SAGE and GAVI.
7. What would be the role of RITAG in terms of advocacy to address financial stability for immunization post-PEI? We should study this strategy, and identify areas where we are lagging behind and discuss at the next meeting.
8. WHO/AFRO will formally notify Polio/Immunization TAG Members and their chairs on the decision made to dissolve these committees.
9. Taking into consideration that a mid-term assessment of the current African Regional Strategic Plan for Immunization in 2017 will be undertaken, RITAG members to take the opportunity to review the current Strategic Plan to determine which areas that need to be strengthened.
10. At the next RITAG Meeting in December 2016, Measles/Rubella elimination goal should be added to the agenda.

2.4 Functioning of RITAG

2.4.1 RITAG Future Working Arrangements & Modalities including RITAG Working Groups

Helen Rees, Chair, RITAG, WHO/AFRO

The key recommendations of the last TFI include: Polio/TAGs remain autonomous from RITAG to be chaired and run by national authorities, while RITAG continues to give advice to WHO Regional Director on overall GPEI progress; nominate an officer to support RITAG, dedicating at least 50% of time to RITAG matters; and, RITAG be more responsive to contingency planning and preparedness to enable WHO to respond well to public health or humanitarian emergencies by proposing to the Regional Director/AFRO recommendations that will enhance contingency planning and preparedness in terms of vaccine development and maintaining immunization services in times of emergencies.

Other recommendations of the last TFI include: the Chair of Regional TAGs (including RITAG) to attend meetings of the WHO/AFRO Independent Advisory Group (IAG) as observers. This would allow Regional TAGs to focus TAG deliberations in line with strategic and policy advice by the IAG; and, update the functions of the RITAG to align with the new strategic directions as outlined in RSPI and GVAP.

She highlighted the mandate of the RITAG. She ended by noting that currently there are four RITAG working groups on country ownership; data quality; demand creation and communications and increasing coverage.

Comments and Observations

1. It was proposed that meetings be fixed for June and December. In addition to this the RITAG have two additional teleconferences between the meetings. The quality of teleconferences should be enhanced.
2. Each time there is an emergency RITAG should meet to define policies for RD.
3. Having meetings in Brazzaville is very important for secretariat support. In the light of this, it was decided that one meeting should be held in Brazzaville.
4. The utility of the four Working Groups will be revisited. TORs and period of performance for the measles TAG will also be considered. If it is measles and rubella and goes into the future, we need to think about how to structure that.

3.0 RITAG MEETING

3.1 Opening

On behalf of Dr Matshidiso Moeti, the Regional Director, Dr Joseph Cabore, the Director of Programmes and Management (DPM), welcomed participants to the meeting. Her absence notwithstanding, she placed high premium on the meeting, and deliver a recorded message.

The RD thanked all Members of the WHO African RITAG for accepting invitation to serve on the RITAG. This is an opportunity to build upon the momentum generated for a lasting impact by ensuring the effective implementation of the signed Addis Ababa Ministerial Declaration. She flagged country ownership, strong political commitment and the active engagement of communities demanding vaccines and immunization services as critical to achieving GVAP goals within the African. She also highlighted integration of activities to support the overall strengthening of the health system.

She also highlighted need to improve data quality, VPD surveillance, surveillance and immunization services in insecure settings. “There is a need to maintain core elements of the polio-funded infrastructure in the post-polio eradication era and I expect to receive constructive advice on the ongoing polio transition planning exercise as well as the feasibility of attaining set goals for special initiatives such as the measles elimination goal set for 2020.”, she added.

She paid a special tribute to Professor Francis Nkrumah, the first-ever Chairperson of the WHO African Task Force on Immunization who, earlier this year, resigned from the African Regional Polio Certification Commission due to personal reasons. In her words, “Professor Nkrumah is a fine scientist of exceptional rigour and self-discipline – virtues which propelled him to the pinnacle of scientific distinction as a professor of paediatrics, and an infectious disease and public health specialist”. She said that it is her honour to recognize Professor Nkrumah in the form of an Award to be presented by the current RITAG Chair – Professor Helen Rees – for his outstanding contribution to immunization within the African Region.

In her remarks, the Chair of RITAG paid glowing tribute to Professor Nkrumah. Two short videos of testimonies of people who have worked with Prof Nkrumah were played. Drs Okwo-Bele and Deo Nshimirimana, who both worked with Prof Nkrumah paid tribute to him. “He is one of those who made the world to believe in Africa”, said Dr Okwo-Bele.

The RD’s award to Prof Nkrumah was handed to the Chair of RITAG by DPM. It will be passed on to Professor Nkrumah.

3.2 Technical Session

Overview

The primary goal for this meeting is to assess the performance of the immunization programme in the African Region in delivering services to protect the African peoples from vaccine preventable diseases; discuss challenges and seek RITAG advice on how to better deliver on the WHO mandate to the people of the region and the world. The focus was on immunization coverage and equity; yellow fever and meningitis as well as vaccine regulation and universal immunization coverage. These were put into a 3-session agenda.

Over 10 presentations were made in plenary, addressing the meeting agenda items. Each presentation comprised the background information, the status of implementation, and the challenges and issues for discussion. The presentations were followed by discussions and actionable recommendations. The presentations, highlights of subsequent discussions and the recommendations are summarized below.

3.2.1 Immunization Overview

Updates on immunization programmes

Updates on immunization coverage and equity in the African Region

Richard Mihigo, IVD, WHO/AFRO

He noted that aim of the 1st ever Ministerial-level conference on immunization in Africa (MCIA) was to secure the commitment of governments and their partners to reach and sustain the required immunization quality and coverage as stipulated in the GAVP and the RSPI. The high point of the conference was the endorsement of the Addis Ababa Declaration on *“Universal Access to Immunization as a Cornerstone for Health and Development in Africa”*. The presentation also noted that Post-MCIA roadmap is currently being developed.

He also highlighted immunization programme performance across the region for different antigens. Of special note, of the 19 countries that have not eliminated maternal and neonatal tetanus, 11 are from the Region. Six of the 11 made good progress and are ready for validation.

The epidemiology of yellow fever is changing, with central and east Africa as areas with new urban outbreaks, high risk of large deadly outbreaks and high risk of national and international spread. The presentation also addressed the control of MenA outbreaks and re-emergence of non-A outbreaks, and challenges of vaccine availability.

He also highlighted government funding of vaccines and routine immunization (See Fig 1).

Comments and observations

1. The impact of outbreaks is massively disrupting. RITAG members noted the impact of the economy in Angola and devolution in Kenya on resource availability.

2. They also noted: data quality problems affecting countries; the need to explore appropriate technology for maintaining cold chain, and tools for reporting; challenges with manufacturing affecting stock-outs; need to work with MPs to mobilizing funding and hold governments to the MCIA commitments.

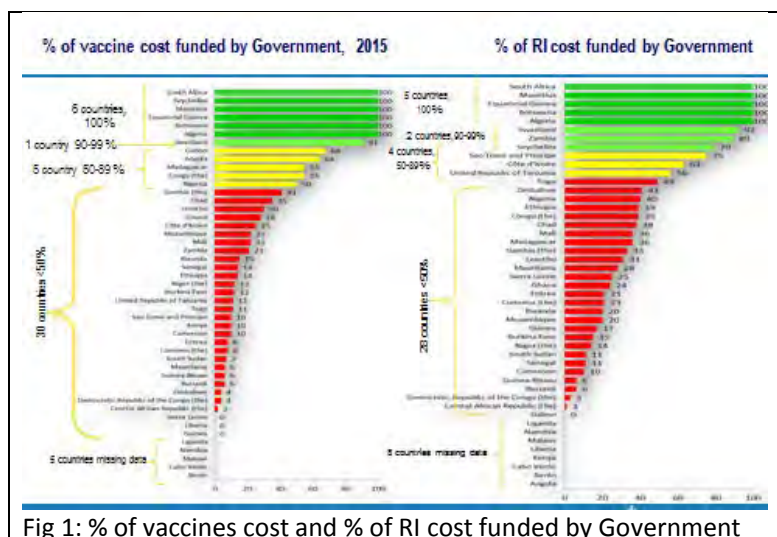


Fig 1: % of vaccines cost and % of RI cost funded by Government

Global overview of polio eradication efforts

Michel Zaffran, POL, WHO/HQ

He provided an overview of the global polio situation, with wild poliovirus type 1 (WPV1) being reported in Afghanistan and Pakistan. Of the 22 circulating vaccine derived poliovirus (cVDPV) cases, 8 were from the African Region. Overall, there has been significantly improved situation with decrease in number of polio cases and environmental samples; and improved access and quality of SIAs. The presentation highlighted four major sources of concern in outbreaks of cVDPV, namely Myanmar, Guinea, Nigeria and DRC.

The presentation addressed the transition planning at country, regional and global levels (See Fig 2).

Comments and observations:

1. The leadership shown by governments and donors should not be allowed to wane; the funding should not be allowed to decline – it should be maintained for routine immunization.
2. The Independent Monitoring Board should continue its work in monitoring progress towards objective 1. The new independent board will focus on objective 4, assessing progress by partners/funders, to ensure enough international attention is put to the transition. Its first meeting will take place in fall 2016.



Fig 2: Transition plan in 16 priority countries

3. IPV production capacity – we expect to have adequate supply by 2017. Companies are being supported to meet demand. In the future OPV will be replaced with several doses of IPV and this manufacturing capacity will be needed.
4. There are areas in Northern Nigeria that have been inaccessible for several years, and the quality of surveillance is uncertain. The virus could be circulating in this area, and the neighbouring countries (Cameroon, Niger).
5. Other countries should publish their experiences with polio eradication as did Nigeria.
6. There is need to recognize that the polio infrastructure has been the backbone for RI for countries, WHO, UNICEF. We cannot underestimate the likely impact of the transition and there will be consequences for many countries' and agencies' ability to conduct surveillance and other key activities.

Progress and dealing with remaining challenges in the African Region

Pascal Mkanda, PEP, WHO/AFRO

The last case of WPV1 was reported in Nigeria in 2014, and WPV3 was last reported in Nigeria in 2012. cVDPV2 was last reported in Guinea in December 2015, and VDPV2 in DRC in March 2016, while a VDPV2 case was reported in Jigawa State, Nigeria in May 2016.

Environmental surveillance in sewage systems isolated cVDPV2 in Borno, Nigeria in March 2016, and VDPV was isolated in Nairobi, Kenya in December 2015 (see Fig 3).

All 47 member states have effectively switched from tOPV to bOPV, while polio-free country documentation was accepted by African Regional Certification Commission, July 2016 (See Fig 4).

Transition mile stones include the finalization of inventory and mapping; finalization of transitional plans and the start of implementation of transitional plans by January 2017.

Comments and observations

1. There are 4 countries that share areas where polio surveillance is

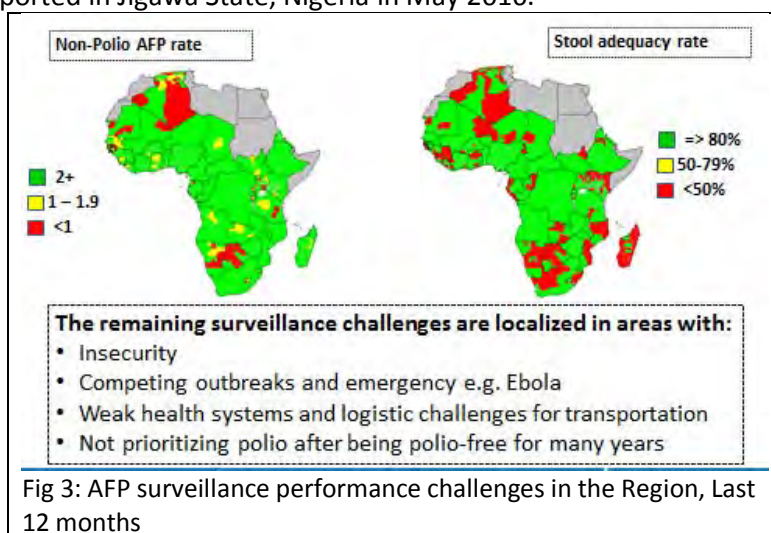


Fig 3: AFP surveillance performance challenges in the Region, Last 12 months

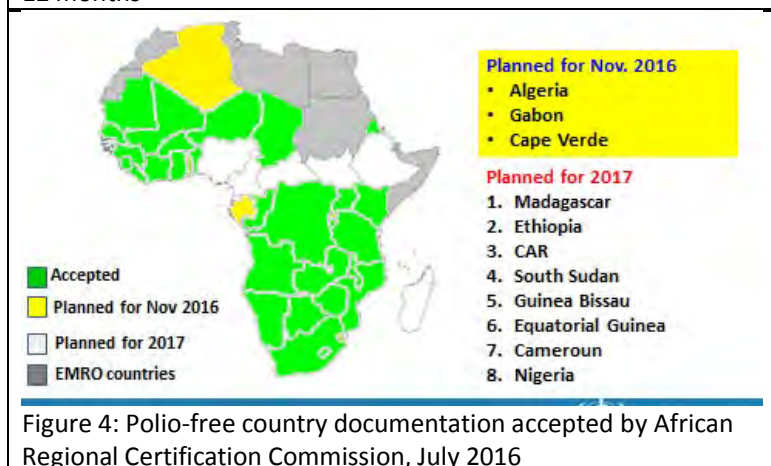


Figure 4: Polio-free country documentation accepted by African Regional Certification Commission, July 2016

weak or not well understood. Immunization activities were integrating surveillance to enhance monitoring of AFP cases in inaccessible areas.

2. We are living through history with the extraordinary achievements. The IPV introduction has been successful, the shortages notwithstanding. The polio strategy has produced best practices we can use for other areas.
3. RITAG needs to look at the country plans for the 16 countries, and advice on funding sources. For polio to be successful, routine immunization must be successful and continue at a very high level. It was also recalled that ministers at the MCIA said they will continue to require donor funding.

3.2.2 Yellow Fever and Meningitis

Yellow Fever in the African Region – an Emerging Public Health Threat

Yellow fever outbreak elimination risk in Africa

Sergio Yactayo, WHO/HQ

Of the 47 endemic countries, 33 are in Africa and 14 in South America. Approximately 897 million people are at risk and >20% (178 million) are in urban areas. In Africa the burden of yellow fever is 84,000 to 170,000 cases and 29,000 to 60,000 deaths. Before 2006, yellow fever outbreaks were uncommon and occurred mainly in West and East Africa. Increasingly Central Africa has been affected.

The success story of the Gambia was highlighted. Following a national Preventive Mass Vaccination Campaign in 1978/79, followed by introduction in RI 3 months later, to date only two cases have been reported in travellers (see fig 5).

Routine EPI is the second pillar for yellow fever outbreak control. Despite this evidence, 11 out of the 34 countries in the yellow fever belt in Africa are yet to introduce the vaccine in the routine EPI.

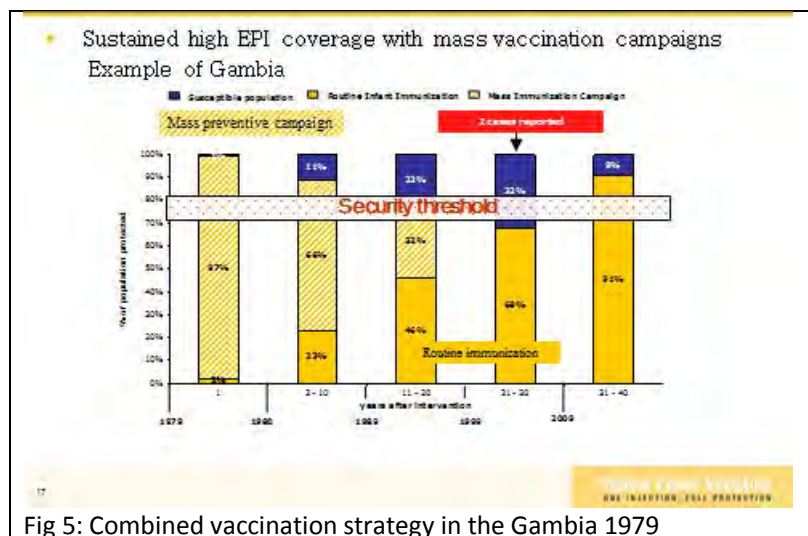


Fig 5: Combined vaccination strategy in the Gambia 1979

Yellow fever surveillance after mass vaccination and vector control

Sergio Yactayo, WHO/HQ

The challenges to yellow fever surveillance include diagnosis that is based on ELISA IgM which persists for 3-5 years; and cross-reactions with other viral infections. Therefore, laboratory confirmation needs to include molecular (< 10 d) and serological methods. Other problems include inability to differentiate IgM from vaccine/wild virus; and the YF case definition that needs to be more specific and include proteinuria. Yellow fever surveillance relied on polio and measles systems. Others strategies include insecticide use (ex. Deltamethrin) could be recommended in some circumstances for urban outbreaks when vaccine is not available or used during a short period of time to decrease vector density.

Comments and Observations

1. The issue of port of entry and transportation of live mosquitoes and larvae through borders was noted. Vectors can be monitored at airports and spraying with pyrethroids is already included in IHR Recommendations). Land borders are very tricky to deal with and require cooperation between countries.
2. YF vector (*Aedes aegypti*) operates during the day, and likes clean water only – so bednets will not work; nets only used over patients to protect others.
3. Limited access to reference laboratories remains a challenge in diagnosis.
4. The rate limiting factor in the use of fractional dose is the availability of syringes. The polio program has a stock pile of 10m syringes, and there are ongoing discussions to see how to use this stock pile.
5. We need to have communities get involved in planning, and response, otherwise they become suspicious and not cooperate.
6. We need a focal person for the response to handle vaccine issues. The stockpile is 6m is inadequate for global needs. About 18 million vaccine doses have been used already this year. We propose to use fractional dose for Angola, and DRC. Each vial will be used for 4 people for practical purposes (not 5).
7. Normally we do response in 7 days – this was not the case in Angola. The political support was not optimal, and the response was not in emergency mode.

Managing the yellow fever outbreak in Angola

Alda Morais De-Sousa, EPI Manager, MoH/Angola

YF vaccine was integrated into Routine EPI in 1980 with low coverage range of 40-77% from 2008-2015. No previous mass preventive YF vaccination campaigns. There are urban and rural breeding sites for *Aedes aegypti* mosquitoes. Mining, agriculture and logging present occupation hazards, and there are primate reservoirs. Past outbreaks in 1971 and 1988 were in Luanda province. Fig 6 shows the distribution of yellow fever

The overall management of the outbreak is coordinated by National outbreak Management Committee, chaired by the Minister of Health. The WHO has established an Incident

management system (IMS) to facilitate the MoH coordination of the international partners' support to the response.

Since the confirmation of the outbreak 13,928,270 doses of YF vaccine was received from ICG. A total of 11,209,178 people were vaccinated in 39 districts in 9 provinces.

Some of the challenges included limited availability of YF vaccines, and language limitation for the provision of technical expertise.

Comments and Observations

1. Diagnosis currently uses PCR – capacity has been enhanced in the country. Most of the probable cases had no or inadequate blood samples to conduct the test.
2. We need to re-define the risk and not rely on the IHR assessment done a while back.
3. At the central level in Luanda and in most districts in Angola there is cold chain capacity. Immunization is conducted after local confirmation of outbreak, and takes 2 months; we have enough time to set up the delivery platforms including cold chain, and the teams.
4. DRC developed a response plan once the epidemic started in Angola. The plan addresses all aspects including immunization, case management, and surveillance.
5. Countries should monitor impact of the outbreak on EPI coverage.
6. The Chair of RITAG noted that epidemiology is changing with global warming, and urbanization. She also noted that there is an opportunity with the dry season. She stressed the need to finish the job in Angola, and do for the DRC geographically targeting. Strategy that has been recommended is RI plus mass campaigns, accompanied with vector control, larvicides, community mobilization, surveillance, improved case diagnosis, and how we address the probable cases. Furthermore she noted that we should anticipate that we are going to see more outbreaks with changing climate, urbanization, slums – 6m dose stock pile is not enough.
7. On the use of fractional vaccine dose this should be carefully studied in populations where it is used to establish longevity of immunogenicity. Regulatory requirements when using fractional doses should be met.
8. We need a focal point for the Africa region for YF given who will anticipate in future outbreak responses.

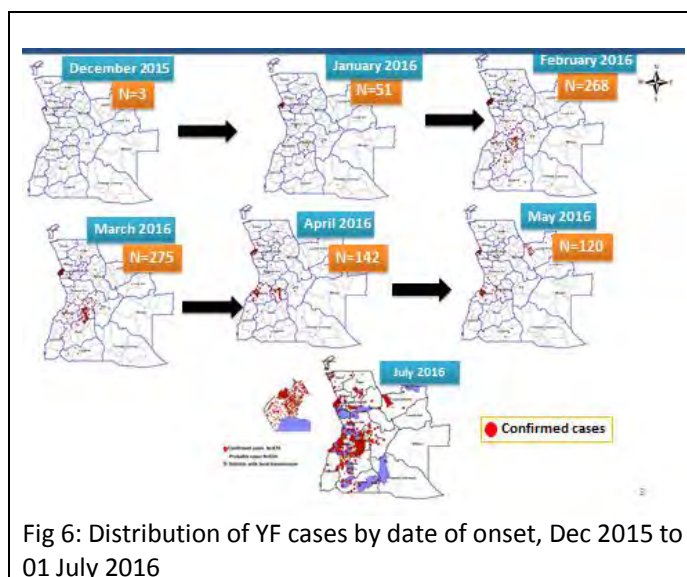


Fig 6: Distribution of YF cases by date of onset, Dec 2015 to 01 July 2016

Preparing for the next Meningitis Season and ensuring Long-term control of Epidemics in the Meningitis Belt Countries

Epidemic meningitis in Africa: epidemiology and control strategies

Andre Bita, WHO Intercountry Support Team for West Africa (IST/West)

A review of the epidemiology of meningitis in Africa shows the peak of cases and deaths was in 2009 when 88,199 cases and deaths were recorded. This was the period immediately before the introduction of MenAfriVac. Following its introduction in 2010, cases and deaths due to meningitis in African have dropped significantly to 30,103 and then declined consistently with increase in vaccination, with only 14,338 cases (all sero-groups) reported in 2016. Meningitis outbreaks between 2009 and 2016 affected mostly Niger, Nigeria and Burkina Faso. See Fig 7.

There were also significant decreases of NmA after the introduction of MenAfriVac in 2010. Only 1 case of NmA in BFA in a vaccinated child aged 8 years old over 46 NmA confirmed in 11 countries that conducted MenAfriVac campaigns.

NmA after 2010 was Sp, NmW, NmC (2015, 2016) and NmC likely due to natural evolutionary changes in the bacterial population, probably not a replacement.

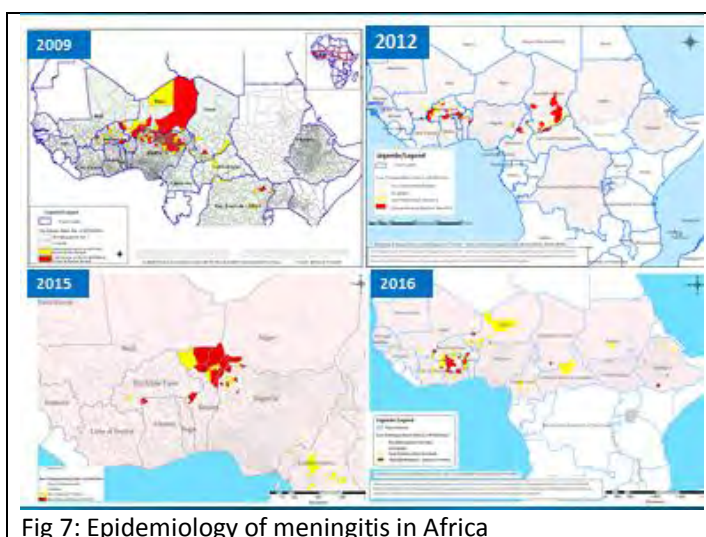


Fig 7: Epidemiology of meningitis in Africa

Challenges with introducing MenAfriVac into routine immunization

Carol Tevi-Benissan, WHO/AFRO

The epidemic meningitis control strategy and MenAfriVac introduction were meant to induce herd immunity against MenA, protect new birth cohorts and enhance surveillance and outbreak response capacity.

Mass vaccination with MenA vaccine was conducted 5 - 6 years ago, targeting 1 -29 year olds, brought almost to zero the risk of meningitis A epidemics. There has however been an accumulation of susceptible populations for NmA (from unvaccinated new born cohorts) from 2010 onwards.

Introduction of routine immunization is key to eliminating risk of NmA outbreaks by targeting these susceptible populations. Fig.8 shows the comparison of scenarios for modelling vaccination strategies with MenA.

The presentation also identified opportunities of MenA transition into routine. It noted that

there exist high community demand for MenA in all countries; an opportunity to catch up on previously missed vaccinations (MCV1, MCV2, Penta, PCV); future vaccines could take advantage of this contact (malaria vaccine in the second and third years of life) and an opportunity to build a stronger second year of life (2YL) platform (spread out the (crowded) immunization schedule beyond infancy?; other healthy child visits in the 2YL (nutrition, Vitamin A, etc).

The next steps include supporting the remaining countries to conduct mass vaccination campaigns (1-29yrs old); support countries to introduce the MenA vaccine into their routine program; and, ensure that countries conduct a one-time mini catch-up campaign for new birth cohorts not eligible for routine.

Responding to non-A meningitis outbreaks

Andre Bitá, WHO Inter-country Support Team for West Africa (IST/West)

Non-A epidemics remain a public health problem with an increase in cases of NmC to more than 2,000 in 2015 (See Fig.9).

Since 2010, with the introduction of MenAfriVac, NmA has been drastically reduced. However, NmW and NmC now constitute threats while *Streptococcus pneumoniae* is priority.

Some of the challenges

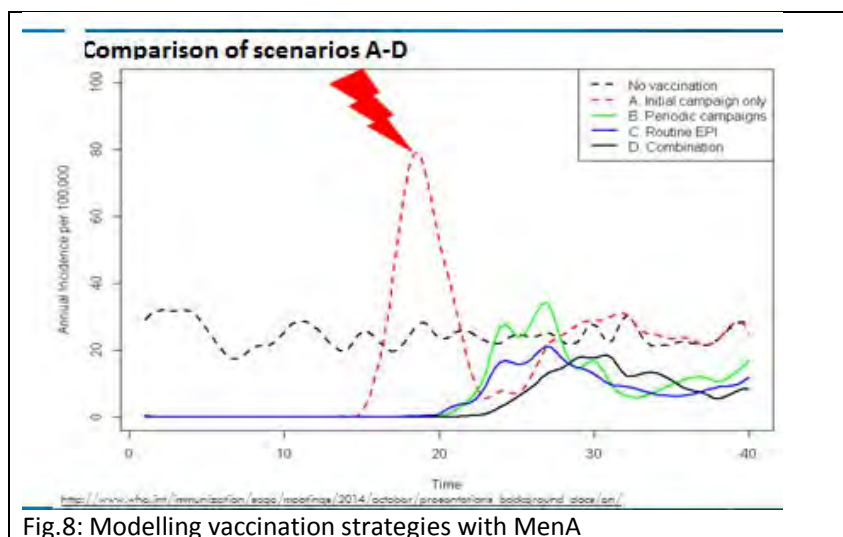


Fig.8: Modelling vaccination strategies with MenA

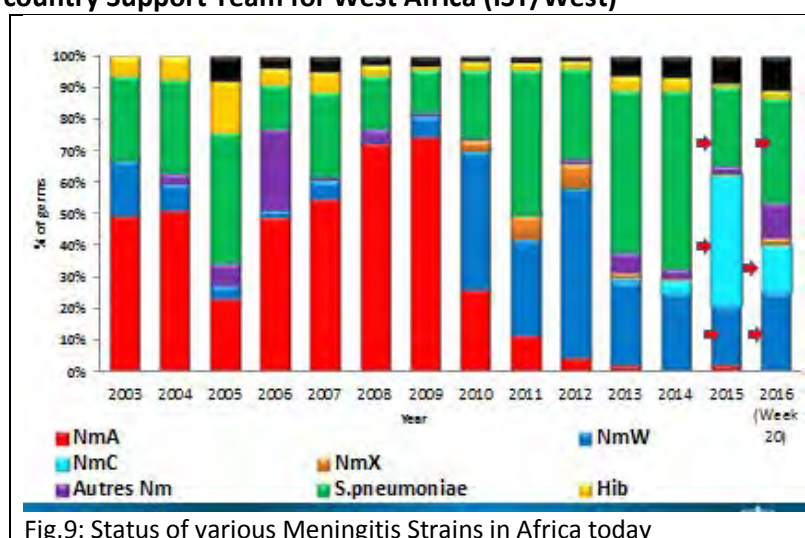


Fig.9: Status of various Meningitis Strains in Africa today

facing the control efforts are vaccine availability; epidemiology of non A meningitis such as the emergence of NmC; and unpredictability of serogroup emergence.

The issues raised for consideration by RITAG were:

1. Other types of pathogens emerging, and the development of affordable polyvalent conjugate vaccine. Should we go for CW, CWA or ACWYX?
2. How do we make a longer term vaccine forecast for reactive vaccination?

Comments and observations

1. The RITAG noted that ACW vaccine from GSK was available in the past as polysaccharide, but is not available in sufficient quantity.
2. The programme moved to case-based surveillance during research phase with MenA; do we still need case-based surveillance or simply use the lab to determine the case mix.
3. It is importance to communicate to communities that the vaccine is only protective against some forms of meningitis but not all.
4. It would be helpful to know the cost of the different valents to guide decisions. However, given the uncertainty around serotype emergence, we may be safer with a broader rather than a narrow option is there is no big difference in cost.
5. There is need for better clarity on the changing sero-type picture – is this replacement or natural emergence as suggested by the presentation.
6. Funding of surveillance is dependent on donors and donors funding can be tough to mobilize. They also noted that a lot has been said about vaccination hardware, now we need to also focus on the software (institutions, communities).
7. Some countries are reluctant with multiple injections but not all. Sometimes it is more the provider and not the mothers objecting. At the global level there is a reflection on how we can use the 2nd year of life for catch-up for those who have missed vaccination in the 1st year. Using this contact can also help with uptake of all vaccines. The 2nd year of life is a good platform given measles is also being given around this time.
8. The Ghana outbreak was mainly among adults and not vaccine eligible children. The serotypes implicated for outbreak in Ghana were serotype 1 (80%) which is in PCV 13; and the 2nd was 12F, and 4% was 35B. Also in the later 90's outbreak in Burkina Faso was predominantly serotype 1.
9. In her summary, the Chair noted that there are clear overlaps with YF, and it could be a good idea to reflect on how we integrate surveillance. She also made reference to the ICG study supported by the Gates Foundation and said that it would be very helpful in untangling the issues; If countries are ok with giving MenA in the 1st year, it was not clear why we should do a 2nd year. If the issue is health workers, then we need health worker education. We need to leverage global health security and advocate for support.

3.2.3 Vaccine Regulation and Universal Immunization Coverage

Vaccine regulation: Regulatory pathways for new vaccines in Africa

Overview of vaccine R&D and regulatory challenges in Africa

Dicky Akanmori, WHO/AFRO, IVD, Brazzaville, Congo

There is now a mosaic of regulations to govern product development & oversight. This creates inefficiency, and adds costs to delivery of new vaccines. Greater harmonization could enhance R&D, reduce costs and timelines. Large portion of R&D budgets are spent on differing regulatory requirements across countries for same therapy, for same disease with no obvious added benefits.

He highlighted the pathway for product development, and the role of the WHO in product development i.e. setting norms and standards based on evidence. He discussed the WHO vaccine preparedness blueprint with illustrations using the target product profiles (TPP) for Ebola vaccines and MERS Cov. He also highlighted vaccine clinical trials that have occurred or planned to occur in Africa.

Major challenges to R&D in Africa were discussed to include few developers of *de novo* products; lack of manufacturing of investigational lots; few sites with capacity for phase 1 trials and large phase 3 trials. He provided updates on the African Vaccine Regulatory Forum (AVAREF) approach to capacity building including: Norms and standards were agreed; Expertise was shared – Ghana hosted review for Sierra Leone; Definition of pathways for approvals of clinical trials; Standard submission; Networking and harmonization; Guidelines and support for review of Clinical Trial Applications and authorization of clinical trials; and, Convenor of joint reviews assisted reviews.

He discussed the vaccine R&D pipeline from the recent PDVAC publications (table 1).

Table 1: New Vaccine Pipeline

Pathogen/Dx	Burden	Status
Respiratory Dx Vaccines		
RSV	No.1 cause of childhood pneumonia	Novavax's RSV F-protein based nanoparticle vaccine most advanced - Phase III started at the end of 2015
GBS	No.1 cause of neonatal sepsis and meningitis	Phase III
Influenza	20.5M cases; 110k deaths among under-5s Under-5s shed virus longer	2012 WHO recommendation to use existing seasonal influenza vaccines
Enteric Vaccines		

Shigella	40% of moderate-severe diarrhea. Leads to severe stunting in 4.6 million children annually	Several candidates in clinical dev't Challenge - multivalent approach, standardized assays needed
ETEC		1 candidate in phase 3, others (1&2) Multivalent approach, standardized assays needed
Norovirus	200,000 deaths annually	Clinical proof of concept done. Entering Phase IIb
HIV	2M new cases; 1.3M deaths	6 efficacy trials in 30 years, best efficacy 31% (RV144) Mutability & genetic diversity of HIV a major challenge
		ALVAC/protein heterologous prime boost in Phase 2 Readout in 2020
Malaria	198M cases; 0.85M deaths	RTS,S/AS01; positive EMA opinion July'15
TB	1.3M deaths	Failure of MVA-85A to show efficacy Early stage translational research and exp medicine
Universal Flu	Hospitalizations in children under 2yr comparable to elderly	PCCs for seasonal influenza vaccines Improved seasonal vaccines in the short term

Overcoming Regulatory challenges in a emergency situation - Phase III clinical trial of a vaccine against EVD: Guinea Country Experience

David Mukanga, WHO AFRO for Binta Bah, DPLM/Guinea

He discussed experiences from the EVD vaccine trial in Guinea. The challenges included: weak ethics and regulatory capacity (lack of clarity on roles between ethics and regulators, unknown timelines for reviews, and unclear Receipt and Review processes for CTA); inadequate resources including expertise; limited data on product for large trial; first ever vaccine clinical trial in Guinea; unusual accelerate product development pathway; complexity of product, and trial design - replication-competent recombinant Vesicular stomatitis virus based vaccine and Ring immunization adaptive design (not regular RCT) respectively; and, the WHO as sponsor of trial.

Approaches used to overcoming the challenges included: country seeking support from the WHO; availability of data from primate and non-primate studies; data from parallel phase 1 trials in Switzerland, Gabon and Kenya conducted rapidly in 2014; NRA established mechanisms for audit of trial and real time evaluation of safety data.

The lessons learnt from the joint assisted review include: Interpretation of benefit and risk differs. NRA did not have model, and relied on external regulatory assistance. But risk/benefit assessment is specific to population of Guinea where there was ongoing EVD outbreak; NRAs deferred this to their experts, when they should be making this decision; Lack of consistency – No reference to past cases or similar products. No desktop guidelines for conducting assessment; Lack of a model – NRA had no model for assessment. No scoring or weighting

system to arrive at decision; Policies/Legal frameworks incomplete; Separation of administrative and scientific functions; Adoption of model for assessment; and, clear roles, responsibilities and information flow.

Regulatory oversight for the development of the first malaria vaccine in Africa: Country perspectives

Edward Abwao, Head, Clinical Trials Unit, KPPB/Kenya

He provided an overview of the Kenya requirements for oversight of clinical trials including the legal provisions. He noted that the RTS,S/AS01 is a complex pre-erythrocytic stage hybrid recombinant protein vaccine, and this was the first time Kenya was processing an application for a vaccine trial.

Other challenges with application included:

- Using a new adjuvant
- A novel delivery system based on the hepatitis B–malaria antigen fusion protein
- There were no AS01 adjuvanted vaccines licensed yet, although MPL is a component of some licensed vaccines e.g (HPV) vaccine
- A phase 3 trial involving a large number of infants and children with the attendant risks (fig 10)
- There were insufficient safety data from earlier trials

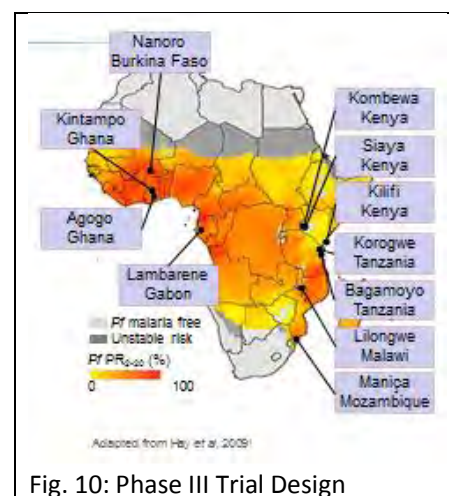


Fig. 10: Phase III Trial Design

To address the challenges, a joint review process was used through AVAREF and lead by the WHO. WHO PATH/MVI facilitated the pre-submission meeting to discuss the requirements for submission. The advantages of the joint review included: increased pool of knowledge and expertise used to evaluate the application; EMA regulators (country of origin of manufacturer) participating in the joint evaluation; African regulators reviewed the application together and learnt from each other (peer learning); first time the both Kenyan ethics and regulators were reviewing a protocol together; as the applicant was present, they were able to answer some of the concerns raised during the review immediately; after review, applicants responded back to PPB for approval (Independence); Sponsor (GSK) responded to each country individually; After the approval, the sponsor submitted the progress reports of the study each year. Amendments, protocol deviation and violations were submitted to PPB; PPB did not conduct any audit, however GSK set up a portal where all safety reports were uploaded and PPB had access; All amendments were reviewed and approved by PPB and PPB also participated JTEG meetings in Geneva that discussed the accumulating data and asked for clarifications on the ongoing clinical trial; at the JTEG meetings, met with other regulatory authorities from Africa and exchanged information on the ongoing study; and, shortening of protocol review and approval period and that JTEG sessions offered a good opportunity to hear, share and seek clarifications on the progress of the study and issues of concern.

In moving forward we need to consider the issue of joint inspections/audits for the trial sites and develop an information sharing portal for multi-centre studies.

Comments and observations

1. There will be future outbreaks & humanitarian emergencies in the African region and that there will be added value to do joint reviews.
2. A working group should be established in the region for product development that supports R&D in emergencies.
3. Giving the perspective of the WHO/HQ, Dr. Okwo-Bele advised that the role of RITAG should pertain to strengthening regulatory activities in the region. A RITAG member should attend each AVAREF meeting to understand what is being discussed, and provide feedback to all RITAG members.
4. For malaria, it was noted that WHO has recommended a pilot study in 3 to 5 countries. Dr. Okwo-Bele then noted that WHO is ready to proceed with a pilot projects in Kenya, Malawi and Ghana for malaria vaccine based on set criteria. Study will be funded by UNITAD and GAVI. The pilot will start in 2017 and early data released in 2019; could eventually lead to roll out of a malaria vaccine in 2022.
5. In terms of African countries, there are a number of countries that have fairly strong regulatory capacities. The size of a country's scientific community is a factor - it varies.
6. The next steps for EVD vaccine, regulatory wise, the intention is for the EUAL to be used as a means for using the product in outbreak circumstances.
7. WHO does plays a great role in capacity building, and as a convener. However, the RITAG concern was raised about WHO drifting to serving as a PI was the case in Guinea.
8. It was also argued that WHO is being proactive – not only EVD but also MenA vaccines. For some of these neglected diseases, the normal way of doing business via pharma does not apply. WHO finds ourselves in a situation where someone has to step-in and we find ourselves in a difficult situation to form a partnership and get the work done.
9. In discussing the role of RITAG in setting the agenda for vaccines development, it was advised that RITAG should look at all potential epidemics in Africa and set up a proactive agenda for Africa and puts pressure to fast track the development of vaccines. The WHO should find ways to claim a space on the global platform for an African voice.
10. There will be an Ebola meeting in September 2016 that will look at vaccines and then report back to SAGE. RITAG needs to get involved in this process and give our opinion. Need to make some recommendations to ensure African representation on global decision-making forums.

Attaining universal access to immunization in the context of universal health coverage Tarcisse Elongo, HSS, WHO/AFRO, Brazzaville, Congo

Immunization is a part of the minimum components of PHC. SDGs (Goal3), target 3.8: Achieve Universal Health Coverage. He illustrated the health system thinking of the immunization system (see Fig.11). He further discussed the problems associated with utilization of services bringing out the equity issues. Some of the challenges to utilization include quality of the services, distances the people have to travel to get services and perennial issues of stock-out of essential supplies due to budget constraints.

As a solution to these challenges, he proposed integration of services, including immunization. He enumerated the attribute of this integration to include robust planning with good alignment, basic package of essential services (sharing human resources, supplies and logistics); own monitoring mechanisms with a system founded information on performance monitoring/management of inputs (quality use).

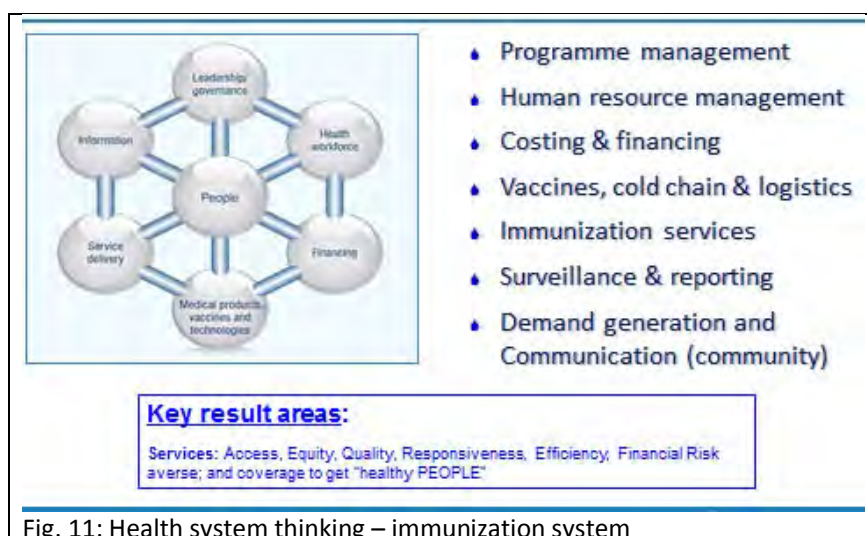


Fig. 11: Health system thinking – immunization system

Examples of integration were mentioned by countries:

- 1) Ethiopia is integrating polio campaigns with other antigens; other maternal services will also strengthen EPI.
- 2) In CAR, EPI campaigns involve ITNs, Vit A, and mainstream. In terms of transport – when district head comes for vaccines, they pick other products for different services. Data is jointly collected using the different tools available and the country is thinking of a single budget at district level, that support all services depending on need.

Comments and observations

1. Decentralization provides opportunity for local planning and integration. RITAG stressed that the integration of planning and service at local level described by countries is very impressive.
2. National and regional levels integration should take on prioritization of vaccines, and other priorities, as prices are an issue especially for the GAVI transitioning countries. Integration is not just integration of activities. It starts with planning, identifying commonalities and then executing together. Not everything can be integrated.
3. The RITAG members further stressed that we do not achieve integration by simply piggy backing one service upon another.
4. It was also noted that several governments think immunization is an issue for WHO/UNICEF/GAVI and not them. It was stressed that the health system should start pushing government to recognize that one day there will not be support from external actors, and we need to start taking leadership now.
5. There is also need to address health expenditure in order to address HSS – if the country's budget is very low, then it becomes difficult. WHO should work with the

World Bank, GAVI to examine public expending, and define a way to improve allocations that allow HSS.

6. Dr Dovlo, the Director of HSS, WHO/AFRO noted that with the Ebola experience, the previous gains varnished; so there is need to build systems that are resilient. There are fundamentals each programme needs to invest in – human resources, core logistics, patient and staff safety, management and accountability specifically at the service delivery level.

WRAP UP AND CLOSURE

In her closing remarks, the Chair thanked everyone present at this meeting for their participation in the very important discussions aimed at advancing the course of immunization programmes in the Region. She expressed her gratitude to RITAG members as well as the WHO Secretariat, and all colleagues in and outside the room who have worked tirelessly to ensure a successful meeting. She also thanked all the colleagues who came from Geneva as well as those from partner organizations for the show of solidarity African member states.

On behalf of the Regional Director, Dr Richard Mihigo, the Manager, Immunization and Vaccine Development (IVD) Programme, thanked the Chair and the RITAG members for finding time to review and guide the Secretariat on its work. He thanked the immunization partners for coming.

He expressed the eagerness of the Region to receive the RITAG recommendations and promised to share them with executive management as well as with EPI managers and other implementation partners.

MINISTERIAL CONFERENCE ON IMMUNIZATION IN AFRICA



STATUS OF IMMUNIZATION IN AFRICA

Africa has made tremendous gains over the last several years in increasing access to immunization. Expanded immunization coverage was largely responsible for a 55% reduction in child deaths across the continent from 1990 to 2012. Despite this remarkable progress, Africa is falling behind on meeting global immunization targets. One in five children in Africa still does not receive all the basic life-saving vaccines he or she needs, and fewer than 15 African countries fund more than 50% of their national immunization programs. The African continent is striving to reach every child with life-saving vaccines, but attaining this goal will require robust immunization systems, active community support and demand, and strong political will.

In February 2016, The World Health Organization's Regional Offices for Africa and the Eastern Mediterranean Regions together with the African Union and the Government of Ethiopia hosted the Ministerial Conference on Immunization in Africa (MCIA) in Addis Ababa, Ethiopia. The conference convened African political leaders and immunization stakeholders to discuss what needs to be done to reach the targets set by the Global Vaccine Action Plan and ensure that all children — regardless of where they are born — receive the full benefits of immunization. With the primary objectives of increasing community demand and building country ownership for immunization, this landmark meeting brought together African Ministers of Health — alongside immunization partners, advocates, technical experts and policymakers from across Africa and around the world — to renew and strengthen commitments to improving access to lifesaving vaccines across the African continent.

MCIA was a galvanizing moment for immunization in Africa, bringing together more than 1,000 stakeholders from approximately 70 countries, including nearly every African country. Two days of in-depth panel sessions, side-events and bilateral meetings focused on: securing sustainable financing, empowering local communities, collecting better data, strengthening immunization systems, and harnessing polio's legacy. Participants advanced critical discussions on immunization progress and challenges, resulting in a Declaration signed by Ministers of Health or heads of delegation from 45 African countries. This historic document is the first declaration focused on immunization signed by African ministers.



World Health Organization





Declaration on "UNIVERSAL ACCESS TO IMMUNIZATION AS A CORNERSTONE FOR HEALTH AND DEVELOPMENT IN AFRICA"

We, African Ministers of Health, Finance, Education, Social Affairs, Local Governments attending the Ministerial Conference on Immunization in Africa, which took place from 24 to 25 February 2016 in Addis Ababa, Ethiopia, convened by the World Health Organization in collaboration with the African Union Commission, are committed to continued investment in immunization programs and a healthy future for all people of the African continent.

Recognizing the tremendous advances that are improving the health of Africa's citizens, including:

- A 50% decline in child death rates, and ever-growing numbers of children attending school;
- Widespread access to vaccines that were not available to African children and adults just a decade ago;
- Higher vaccine coverage rates across the continent in each five-year periods between 1999-2014;
- The remarkable achievement of the Africa continent for interrupting wild poliovirus transmission for more than one year; achieving near elimination of Meningococcal meningitis A epidemics, and the significant reduction in disease burden and mortality due to measles.

Bearing in mind the recently ratified Sustainable Development Goal target of Universal Health Coverage which calls for access to immunisation for all (New York, September 2015); and that health is fundamental to social and economic development;

Acknowledging that, broad-based, inclusive growth in Africa is dependent on a healthy population; and that strong immunization programs are a cornerstone of robust systems that help achieving universal health coverage, which is critical to helping national leaders achieve their economic and development goals;

Reaffirming the economic imperative and benefits of reducing vaccine-preventable diseases and consequential deaths, which will improve overall health, empower our future generation and allow every person to achieve his or her full potential;

Recalling the Heads of State Declaration on Polio Eradication in Africa: "Our Historic Legacy to Future Generations" (Johannesburg, June 2015); the World Health Assembly resolution (WHA68.6) on the Global Vaccine Action Plan (Geneva, May 2015), the commitment made by African Ministers of Health on Universal Health Coverage in Africa (Luanda, April 2014); the Immunize Africa 2020 Declaration (Abuja, May 2014) endorsed

by African Heads of State; the World Health Assembly resolution that commits all 194 Member States to apply the vision and strategies of the Global Vaccine Action Plan (GVAP) (Geneva, May 2012), and the African Heads of State endorsement of the Pharmaceutical Manufacturing Plan in 2012 as the framework for African people to have access to essential, quality, safe and effective medical products and technologies.

Recognizing that despite progress, universal access to immunisation by 2020, as endorsed under the GVAP, is largely off track in Africa as indicated by the 2014 GVAP report; but that with resolve we can still achieve the GVAP target of at least 90% coverage in our countries and at least 80% coverage in every district for all nationally available vaccines;

Admitting that to sustain the progress made in vaccine introduction and coverage — and achieve the full potential to save children's and adult's lives — current national budgetary allocations to vaccination programmes within the context of national health systems financing will need to be further increased;





We hereby collectively and individually commit ourselves to:

- Keeping universal access to immunisation at the forefront of our efforts to reduce child mortality, morbidity and disability, and in doing so help our countries achieve their long-term health, economic and development goals;
- Increasing and sustaining our domestic investments and funding allocations, including innovative financing mechanisms, to meet the cost of traditional vaccines, fulfil our new vaccine financing requirements, and providing financial support for the operational implementation of immunization activities by EPI programs;
- Addressing the persistent barriers in our vaccine and healthcare delivery systems, especially in the poorest, vulnerable and most marginalized communities, including the strengthening of data collection, reporting and use at all levels as well as building effective and efficient supply chains and integrated procurement systems;
- Increasing the effectiveness and efficiency, as well as changing the approaches as needed, of our immunization delivery systems as an integrated part of strong and sustainable primary health care systems;
- Attaining and maintaining high quality surveillance for targeted vaccine preventable diseases.
- Monitoring progress towards achieving the goals of the global and regional immunization plans
- Ensuring polio legacy transition plans are in place by end-2016 that will allow future health programs to benefit from the knowledge and expertise the polio program has generated through the eradication initiative;
- Developing a capacitated African research sector to enhance immunization implementation and uptake;
- Building broad political will, working with communities, civil society organizations, traditional and religious leaders, health professional associations and parliamentarians, for the right of every child and every community to have universal access to life-saving vaccines, and by extension the best possible chance for a healthy future;
- Promoting and investing in regional capacity for the development and production of vaccines in line with the African Union Pharmaceutical Manufacturing Plan including the strengthening of national regulatory authorities.

WE CALL UPON:

- Member states and partners, including African development banks and African regional economic communities, to support the implementation of this Declaration, and to increase their efforts to mobilize resources and secure new investments to strengthen national immunization programmes to achieve the GVAP goals and overall health care delivery systems in the Member States;
- Member states and partners, to negotiate with vaccine manufacturers to facilitate access to available vaccines at affordable prices, and in increasing price transparency as well as developing price databases in line with resolution WHA68.6;
- Gavi, the vaccine alliance to consider refugees and internally displaced populations as eligible recipients of Gavi support for vaccines and operational costs;
- The World Health Organization and the African Union Commission to support member states to share experiences, strengthen capacity, and establish mechanisms for monitoring progress towards the fulfilment of these commitments.

We thank his Excellency Hailemariam Dessalegn, Prime Minister of the Federal Democratic Republic of Ethiopia, and host country for this Ministerial Conference on Immunization in Africa, for agreeing to champion this declaration and further request him to present it to the African Heads of States at the 26th Summit of the African Union, to be held in June 2016.

THE ADDIS DECLARATION ON IMMUNIZATION HAS BEEN SIGNED BY 45 COUNTRIES TO-DATE.



A NUMBER OF CONSTITUENCIES DEVELOPED AND SIGNED STATEMENTS SUPPORTING THE ADDIS ABABA DECLARATION. THESE INCLUDE:



**Civil Society
Organization
leaders**



**Religious
leaders**



Parliamentarians



First Lady of Ethiopia
on behalf of the Organization
of African First Ladies
Against HIV/AIDS

For more information, please visit www.ImmunizationinAfrica2016.org

Ad-hoc Virtual TAG Meeting 2016

**XXIV Meeting of the Technical Advisory
Group on Vaccine-preventable Diseases**

**May 13, 2016
Washington, DC, USA**



**Pan American
Health
Organization**



**World Health
Organization**
REGIONAL OFFICE FOR THE Americas

Table of Contents

TABLE OF CONTENTS.....	2
TAG MEMBERS	3
ACRONYMS.....	5
INTRODUCTION	7
GLOBAL IPV SUPPLY SITUATION: HOW TO MANAGE THE LIMITED IPV SUPPLY AND DEAL WITH POTENTIAL STOCKOUTS	8
RECOMMENDATIONS	10
USE OF THE DENGUE VACCINE IN ROUTINE IMMUNIZATION.....	13
RECOMMENDATIONS	15
FEASIBILITY OF PERINATAL HEPATITIS B ELIMINATION IN THE AMERICAS	16
RECOMMENDATIONS	18
EXTRA AGENDA TOPICS	19
TERMS OF REFERENCE FOR THE TAG.....	19
YELLOW FEVER	19

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*** Not present at Ad-hoc TAG 2016**

Acronyms

AFRO	WHO Regional Office for Africa Region
AFP	Acute Flaccid Paralysis
BCG	Bacillus Calmette-Guérin (vaccine against severe forms of tuberculosis)
bOPV	Bivalent Oral Poliovirus Vaccine
CI	Confidence Interval
cVDPV	Circulating Vaccine-Derived Poliovirus
CYD-TDV	First Dengue Vaccine Introduced in the Market
DTP	Diphtheria-Tetanus-Pertussis Vaccine
EMA	European Medicines Agency
EMRO	WHO Regional Office for the Eastern Mediterranean Region
EMTCT	Elimination of Mother-to-Child Transmission
EURO	WHO Regional Office for European Region
fIPV	Fractional Dose of the Inactivated Polio Vaccine
GHSS	Global Health Sector Strategy
HBeAg	Hepatitis B “e” Antigen
HBIG	Hepatitis B Immune Globulin
HBsAg	Surface Antigen of the Hepatitis B Virus
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HIV	Human Immunodeficiency Virus
ID	Intradermal
IM	Intramuscular
IPV	Inactivated Polio Vaccine
mOPV	Monovalent Oral Poliovirus Vaccine
mOPV2	Monovalent Oral Poliovirus Vaccine Type 2
MTCT	Mother-to-Child Transmission
NRA	National Regulatory Authorities
OPV	Oral Poliovirus Vaccine
OPV2	Oral Poliovirus Vaccine, Second Dose
PAHO	Pan American Health Organization
RF	Revolving Fund
SAGE	Strategic Advisory Group of Experts on Immunization of the World Health Organization
SEARO	WHO Regional Office for the South-East Asia Region
STI	Sexually-Transmitted Infections
TAC	PAHO Hepatitis Technical Advisory Committee
TAG	Technical Advisory Group on Vaccine-preventable Diseases
tOPV	Trivalent Oral Poliovirus Vaccine

UNICEF	United Nations Children's Fund
VDPV	Vaccine-Derived Poliovirus
VDPV2	Vaccine-Derived Poliovirus Type 2
WHA	World Health Assembly
WHO	World Health Organization
WPRO	WHO Regional Office for the Western Pacific Region
WPV2	Wild Poliovirus Type 2

Introduction

On May 13, 2016, technical staff from PAHO met with members of the TAG for an ad-hoc virtual meeting. The discussion during this meeting included three topics: the global shortage of IPV, use of the dengue vaccine in routine immunization and the feasibility of eliminating perinatal Hepatitis B in the Region of the Americas. Dr. Cuauhtemoc Ruiz Matus welcomed the TAG members and attending staff and gave the word to TAG chair Dr. Peter Figueroa. Dr. Figueroa expressed that the global IPV shortage was the main reason behind calling the meeting, as it is an urgent matter that should be effectively addressed in the Region. A brief update on the current status of yellow fever globally and in the Region was also given at the meeting, as well as an update on the Terms of Reference for TAG members.

Although virtual technical meetings had been successfully conducted in the past, this was the first time that a virtual TAG meeting was held. TAG members acknowledged the versatility of this type of TAG session. Virtual ad-hoc TAG meetings will be conducted in the future, especially if another urgent matter for discussion becomes known.

Global IPV Supply Situation: How to Manage the Limited IPV Supply and Deal with Potential Stockouts

Background

In May 2012, the World Health Assembly declared the completion of polio eradication as a “programmatic emergency for global public health.” On 25 January 2013, the Executive Board of the World Health Organization (WHO) approved the targets, goals, and timelines of the Polio Eradication and Endgame Strategic Plan 2013-2018, which seeks to simultaneously eradicate wild poliovirus and eliminate vaccine-derived poliovirus (VDPV). The main objectives of this Strategic Plan are to detect and interrupt poliovirus transmission; to strengthen immunization programs and withdraw the oral poliovirus vaccine, commencing with the withdrawal of the type 2 component by switching from the trivalent (serotypes 1, 2 and 3) to the bivalent (serotypes 1 and 3) vaccine; to contain poliovirus and certify the interruption of transmission; and to plan how to utilize the legacy of the fight against poliomyelitis.

For the globally synchronized switch from the trivalent to the bivalent oral poliovirus vaccine, WHO recommended that all countries using only the oral poliovirus vaccine (OPV) introduce at least one dose of the inactivated polio vaccine (IPV) into their routine vaccination programs to ensure that new cohorts of newborns have some protection against the type 2 poliovirus, either wild or vaccine-derived. In April 2014, the Technical Advisory Group (TAG) on Vaccine-Preventable Diseases of the Pan American Health Organization (PAHO) recommended that the countries should consider a sequential schedule. Ideally, countries should consider two IPV doses followed by two OPV doses. However, if a country is considering only one IPV dose, this should be with the first dose of the DTP-containing vaccine and followed by three OPV doses.

Due to the very limited supply of IPV, in order to ensure that all countries in the Region would have access to IPV before the switch, PAHO made an agreement with the countries that participate in the Revolving Fund (RF) to introduce only 1 dose of IPV, preferably in the second semester of 2015, in a schedule of one dose of IPV followed by 3 or 4 doses of OPV, until the IPV supply is sufficient to meet the real demand of all countries. Nonetheless, global supply of IPV continues to be insufficient and not timely and the availability of IPV is expected to remain constrained until the end of 2017.

In October 2015, the Strategic Advisory Group of Experts on Immunization of the World Health Organization (SAGE) reaffirmed that the withdrawal of OPV2 should proceed in April 2016, even in countries where IPV introduction will be delayed, due to the fact that the public health risks associated with the continued use of the type 2 component in tOPV far outweigh the risk of new VDPV2 emergence after use of OPV2 is stopped. The bOPV supply is sufficient to meet the global demand.

Risk of VDPV emergence

Based on the mathematical models considered, there is expected to be at least 1-2 cVDPV type 2 outbreaks within the first 12 months following the switch, with Pakistan representing a high-

risk area. The risk is greatest in the first year and declines thereafter; however, the consequences are expected to be greater the longer the interval between the switch and the emergence, particularly in areas where IPV coverage is not equal to or greater than 95%.

It is important to highlight that IPV has only a limited role in preventing the emergence of VDPV type 2. IPV's primary value is in minimizing the occurrence of paralytic disease from any WPV2 or VDPV2 after the switch. However, if a type 2 outbreak emerges post-switch, it would be rapidly controlled with the monovalent oral poliovirus vaccine type 2 (mOPV2), as the population would have already received at least one IPV dose and therefore would already have some degree of immunity.

Global IPV supply situation

The level of commitment from countries to meet the IPV introduction timeline was exceptional. Out of 126 planned introductions, 100 countries have introduced IPV as of 1 May 2016. In the Americas, all of the 36 countries that had previously used only OPV have already introduced IPV in their routine immunization schedule. Unfortunately, the rapid scale-up of IPV production required has encountered multiple challenges, leading to a global shortage. Current constraints mean that approximately 20 countries, from AFRO, EMRO, EURO and WPRO, which have not already received their first IPV shipment through UNICEF and are considered at low risk for circulating vaccine-derived poliovirus (cVDPV) type 2 outbreaks, will not be able to introduce IPV in 2016. These countries are expected to receive their first IPV shipments in the fourth quarter of 2017. In addition, shipments to approximately 25 countries, from AFRO, EMRO, SEARO and WPRO that have already introduced IPV and are considered at low risk for type 2 outbreaks, will not receive additional supply before the fourth quarter of 2017.

Update of IPV supply situation in PAHO Region

Currently, the PAHO Revolving Fund only procures IPV through one manufacturer, Bilthoven Biologicals, from The Netherlands. This supplier has reduced the quantity offered to the RF due to production issues in 2016. Additionally, scheduled deliveries have been delayed. The first deliveries for 2016 are only expected from September 2016 onwards, and there are outstanding orders from the 2015 plan, totaling 1.4 million doses, which will hopefully be delivered through August 2016.

The only other possible IPV manufacturer, who in addition to not accepting the conditions set by the RF, has also progressively been reducing the supply of this vaccine to UNICEF. Furthermore, the RF has accepted a small availability of doses in pre-filled syringes for a couple of countries to diminish the supply gap. No additional sources of supply exist globally.

Supply perspective

The PAHO Revolving Fund has been working closely with the manufacturer to stay up to date on any potential further setbacks and has been adapting the IPV allocation and delivery plans, prioritizing countries that are in the greatest need to avoid stockouts. Despite the efforts, one country is facing a stockout and 5 additional countries could face the same situation if the manufacturer performance continues to deteriorate. Considering this production performance, the Region must be prepared to face country stockouts, varying from a few weeks to several

months. This risk will last through the end of 2017, until additional production capacity is available.

Fractional dose schedules

There is a growing body of scientific evidence on the safety and immunogenicity of intradermal (ID) fractional IPV (fIPV) dose administration, which delivers 0.1ml or 1/5 full intramuscular (IM) dose. Studies have been conducted for ID fIPV-dose as primary series in routine immunization schedules, as well as for boosting.

In March of this year, the WHO updated the Polio Position paper, which includes a recommendation to face the global IPV shortage, recommending that: *“As an alternative to the intramuscular injection of a full dose of IPV, countries may consider using fractional doses (1/5 of the full IPV dose) via the intradermal route, but the programmatic cost and logistic implications of this option should be considered. The SAGE working group in March 2016 confirmed that the proposed schedule of two ID fIPV can induce equal or better immunity than the current one full-dose schedule.”*

The SAGE working group, in March 2016, confirmed that the proposed schedule of two ID fIPV doses can induce equal or better immunity than the current one intramuscular full dose schedule.

While the use of mOPV is the mainstay of an outbreak response, there are some special recommendations for ID fIPV use in outbreak response. The SAGE working group, in January 2016, recommended that ID fIPV should be used for outbreak response. They reaffirmed this recommendation in March 2016, adding that fractional IPV provides good seroconversion in naïve infants, prevents paralysis and boosts humoral immunity in previously OPV-vaccinated children.

Recommendations

The TAG reiterates its concern about the insufficient global supply of IPV and recognizes that the RF and the Immunization Unit are closely monitoring the situation and adjusting IPV delivery schedules in order to avoid stockouts in countries of the Region.

Due to the overall global deficit of IPV that will last through 2017, the TAG recommends that countries:

1. Reduce IPV wastage

- Ensure strict adherence to the vaccination schedule, using IPV only with children that have turned two months of age after the official introduction date of IPV in the country.
- Fully implement the WHO open vial policy, which permits the use of open vials of IPV for up to 28 days, provided that the defined criteria are met as outlined in the [WHO policy on the use of opened multi-dose vaccine vials](#).
- To reduce wastage of the vaccine, avoid, whenever possible, the use of IPV in extramural activities, prioritizing vaccination strategies that use fixed or mobile vaccination posts.
- Closely monitor IPV supply in the country to assure that all services are supplied and all possible service points that could have excessive vaccine wastage are identified, for providing appropriate recommendations.

2. Prepare to respond to possible IPV shortages

- All health workers should be informed about a possible shortage of IPV and prepared to respond to this eventuality.
- In the absence of IPV for administration as the first dose of vaccination against polio, children should receive bOPV as the first dose in the schedule. In these cases, IPV should be applied at the first contact as the second, third or booster dose in the schedule, always respecting the minimum interval of 4 weeks between doses of polio vaccines.
- Due to the uniqueness of this recommendation, it is necessary to inform all vaccinators about the importance of clearly registering which vaccine was used, in both the national registry and on the child's vaccination card, so that for the next visit, it will be clear if the child has already received a dose of IPV or if this dose is still pending.

3. Prepare to respond to polio outbreaks

- All countries should review their polio outbreak response plans, considering the guidelines presented in the documents published by the Global Polio Eradication Initiative, on 20 April 2016: Standard Operating Procedures for responding to poliovirus events and outbreaks, Part 1: General Standard Operating Procedures, and Part 2: Specific protocol for type 2 poliovirus (both available on the PAHO website: www.paho.org/polio).
- Countries should ensure that they can receive mOPV2 in a very short time from the global stock pile for outbreak response, which will be sent through UNICEF.
- IPV will not be needed to respond to all type 2 polio outbreaks. However, if it is assessed that IPV use is necessary, the WHO recommends that countries use fractional doses, administered intradermally, to make sure there is sufficient supply to serve all countries in need.
- Countries should evaluate their capacity in terms of skilled human resources to implement a vaccination campaign with fractional doses of IPV administered intradermally. Furthermore, countries should ensure that they can use the IPV vaccine this way, as recommended by the WHO for outbreak response. The recommendation is based on scientific evidence, but it is not indicated so on the vaccine inserts, therefore that means that countries must use fractional IPV as off label use.

4. Evaluate the capacity for use of ID fIPV in routine program, if needed

- At this time TAG does not recommend that countries begin an ID fIPV schedule, but this option could be considered if the supply situation continues to worsen.
- Another TAG meeting should be convened if there is a change in the current IPV supply situation that justifies further assessment and recommendations.
- In the meantime, all countries should begin to evaluate the capacity of the program to implement an ID fIPV schedule. This includes evaluating the availability of trained personnel to apply ID vaccine, BCG syringes, programmatic cost and feasibility. Also, countries should evaluate if any changes need to be made to the national registry system.
- Due to the fact that the ID fIPV recommendation is based on scientific evidence, but is not included in the vaccine inserts, countries should ensure they can use ID fIPV off label.

5. Strengthen surveillance

- The TAG reiterates that due to the risk of the emergence of cVDPV type 2 in the post-switch period, all countries must maintain sensitive surveillance systems in order to rapidly detect and interrupt any type 2 circulating poliovirus.
- Countries should strive to meet the following AFP quality surveillance indicators:
 - 1 AFP case per 100,000 children less than 15 years old
 - > 80% cases with adequate samples
 - > 80% cases investigated within 48 hours or less

Use of the Dengue Vaccine in Routine Immunization

At the last meeting of the TAG held in Varadero, Cuba in July 2015, an update on the current status of dengue vaccine development was presented and discussed. Based on knowledge about the research and development pipeline for dengue and the data available on the only product near marketing launch at the time, the TAG recommended the following:

1. TAG recommends that the countries swiftly implement an integrated approach to prevention, control and case management of dengue, as stated in the World Health Assembly Resolution (2015).
2. While the burden of dengue in the Americas is important, TAG notes there is insufficient evidence to make a recommendation on vaccine introduction at this time. TAG itself is committed to considering timely new evidence as it becomes available and countries should do the same over the coming months in their own national decision-making processes.
3. In coordination with other initiatives, PAHO's ProVac Initiative should support national level decision-making through the use of economic evaluations grounded in local data.

As noted in the TAG of Cuba, introducing the dengue vaccine is part of the Global Strategy for the Prevention and Control of Dengue (2012-2020). Given the importance of having a preventive vaccine against this disease, the Strategic Advisory Group of Experts on Immunization (SAGE) established a workgroup comprised of dengue experts in March 2015.

CYD-TDV – a quadrivalent vaccine – (Dengvaxia of Sanofi Pasteur) is the first dengue vaccine candidate to come to the market. The live attenuated vaccine is already registered in five countries (Mexico, Brazil, El Salvador, Paraguay and the Philippines) globally. It has been registered for use among people aged 9 to 45 or 9 to 60 years and requires a 3-dose series given at 0, 6 and 12 months. It is also in the process of being registered in other countries.

In Latin America, CYD-TDV was first registered in Mexico in December 2015 for use among people aged 9 to 45 living in endemic areas. Registration at the country-level implies that the product can be locally marketed and sold. However, a NRA decision to license a biologic is separate from the decision to incorporate a product into a routine public health program.

Besides the CYD-TDV product, there are an additional 5 vaccines that are currently being evaluated in different phases of clinical trials. The CYD-TDV vaccine is not prequalified by the WHO yet. Prequalification requires registration by the NRA of the country in which the vaccine is made (in this case, EMA - European Medicines Agency). The WHO is waiting for the submission of a request by the manufacturer to initiate the prequalification process.

According to the information generated by the CYD-TDV vaccine phase III studies:

- SAGE reviewed the evidence generated by two major phase III studies:
 1. People 2-14 years of age in 5 countries in Asia
 2. People 9-16 years of age in 5 countries in Latin America

- The efficacy of the vaccine depends on several factors:
 1. Type of strain: greater protection against the type 3 and 4 than against type 1 and 2.
 2. Age: greater protection in older children.
 3. Severity of disease: greater protection against serious and hospitalized cases.
 4. Serologic status of individual at time of vaccination: complete protection was achieved only in participants with previous exposure to dengue virus.

The efficacy of the vaccine evaluated 25 months after the first dose among ages 9 to 16 years in both clinical trial studies was 65% (95% CI 60.7 - 69.9).

The protection response was different for the 4 dengue serotypes. For types 1 and 2, 50% and 42% of individuals were protected, respectively, and for the serotypes 3 and 4, 74% and 77% of individuals were protected, respectively.

In Asia, it was observed that children initially immunized at 2 to 5 years of age, showed a statistically significant increase in the risk of hospitalization due to dengue in the third year after the first dose, although, this risk disappeared in the 4th and 5th year. The biological explanation of this situation has not yet been determined, but may be related to the first exposure to the vaccine and/or age. This situation was not observed in the age group of children >5 years of age.

In general, phase III clinical trial results conducted in Asia and Latin America have shown that the CYD-TDV vaccine is effective, providing protection against all 4 serotypes of the dengue virus and that it has an acceptable safety profile. However, the local epidemiology and distribution of serotypes pre-vaccination appears to affect the overall efficacy of the vaccine.

The SAGE also considered the results of a comparative modeling analysis that evaluated the potential public health impact of introducing the CYD-TDV in a routine program, which was performed by 7 different teams. The results from the different modeling groups were consistent in their conclusion: in places of high transmission, the introduction of this vaccine at the beginning of adolescence could reduce dengue fever-related hospitalization by 10-30% in a period of 30 years. This represented a substantial health benefit. However, the modeling analysis determined that the vaccine might be less beneficial in places with low transmission, due to the high proportion of seronegative individuals, leading to a minor protective effect.

With this information the SAGE recommended that:

- Countries consider the introduction of the CYD-TDV only in places (national, sub-national level) with high endemicity (seroprevalence $\geq 70\%$ in the target population group for vaccination or other epidemiological marker).
- In highly endemic areas (seroprevalence at 9 years of age approximately 90% or more), vaccination at the age of 9 years old will have the greatest impact. On the other hand, in places where the seroprevalence at 9 years of age is less than 90% (but greater than 50%), vaccination at age 11 to 14 years is advisable.

- Optimal protection requires a series of 3 doses given at 0/6/12 months. However, more evidence will be needed to understand if a simplified schedule may allow similar or better levels of protection.
- The currently available vaccine is restricted for use in ages 9 to 45.
- The target group for vaccination should be defined by each country on the basis of an analysis of the endemicity of dengue and programmatic feasibility.
- Due to an increase in the risk of hospitalization in children 2 to 5 years of age, it is not recommended that this vaccine be used in children younger than 9 years old, which is indicated by the manufacturer in the product insert.
- It is not recommended as an emergency response tool in outbreaks.
- Co-administration with other vaccines is not recommended since data on safety and immunogenicity in these conditions is not yet available.
- The introduction of the vaccine against dengue must be part of a comprehensive integrated control strategy, including strengthened vector control, case management and surveillance.
- The decision about the introduction of this vaccine – as has been done in the past – requires a thorough country-level assessment, including consideration of the national and local priorities, the epidemiology of the disease, predictive impact, cost-effectiveness and affordability and budgetary impact.

Recommendations

- Given the conditions for the use of this vaccine and the lack of evidence on some aspects of safety and effectiveness, PAHO's TAG reaffirms the prior recommendation made in July 2015 and does not recommend the introduction of the dengue vaccine into routine national immunization programs at this time.
- Countries should strengthen surveillance in order to better understand dengue disease burden. This is especially important in the context of outbreaks of vector-borne diseases like Zika and Chikungunya.

Feasibility of Perinatal Hepatitis B Elimination in the Americas

Hepatitis B virus (HBV) infection is a leading cause of infectious disease mortality worldwide with an estimated 4 million new HBV infections and 780,000 deaths annually. It is preventable with vaccination. The World Health Organization (WHO) estimates that worldwide more than 2 billion people are infected with HBV, of whom 240 million have a chronic infection. Most HBV-related morbidity and mortality result from complications of chronic infection: cirrhosis and hepatocellular carcinoma (HCC). It is estimated that 15-25% of people with chronic HBV infection will die prematurely from HBV-related cirrhosis or HCC.

The risk of chronic infection is inversely related to the age at infection. Chronic infection develops in up to 90% of infants infected during the perinatal period, 20-60% of young children infected in the post-perinatal period through five years of age, and in <5% of children, adolescents, and adults with infections acquired after five years of age. Globally, two-thirds of HBV-related deaths result from infection acquired in the perinatal and early childhood period.

According to a recent review, approximately 7.4 million people are living with chronic HBV infection in the Americas. The regional average of HBV seroprevalence is 0.81%, however in highly endemic areas, such as the Amazon basin, the prevalence of HBV infection is over 8%. In regions of low endemicity, including the United States and parts of South America, HBsAg prevalence is less than 2% and other areas in Latin America have intermediate prevalence (between 2% and 4%).

The WHO is currently developing a 2016-2021 Global Health Sector Strategy (GHSS) on viral hepatitis, with the plan to submit it to the 69th World Health Assembly in May 2016. The GHSS responds to specific requests included in resolution WHA67.6 of 2014, asking the WHO to assess the feasibility of eliminating HBV infections as a public health problem. The 2016-2019 Regional Plan for Viral Hepatitis presented and endorsed by a Directing Council Resolution in 2015 is fully aligned with the WHO's perspectives and includes targets, activities and interventions specific to the elimination by 2030, with EMTCT of HBV integrated into the existing platform for HIV and syphilis.

The WHO is promoting the elimination of HBV infection by the year 2030. The feasibility of HBV elimination was determined through modeling studies. The results of these studies were used to set the targets that include eliminating HBV by 2030 through a combination of high routine 3-dose infant vaccination coverage, high birth dose coverage, and the scale up of treatment services for persons with chronic HBV infection.

Currently, WHO and SAGE recommendations to reduce perinatal and early childhood transmission emphasize the importance of a birth dose of hepatitis B vaccine administered within 24 hours of birth, followed by two or three doses to complete the series. PAHO Regional Immunization Action Plan (2016-2020) presented to the Directing Council in September 2015

includes these recommendations and specific indicators to monitor the progress made by countries.

In the Americas in 2014, regional coverage with three doses of the hepatitis B vaccine among children less than one year of age was 89%. It is important to highlight the progress made on birth dose introduction in the national infant immunization schedules from 18 countries in 2013 to 27 countries in 2016. Regional coverage with the Hepatitis B birth dose is 81% (source: WHO/UNICEF Joint Reporting Forms/Country Survey).

Regarding the use of Hepatitis B immune globulin (HBIG) prophylaxis in conjunction with HBV vaccination, this may offer a minimal additional benefit to newborn infants whose mothers are HBsAg positive, particularly if they are also hepatitis B “e” antigen (HBeAg) positive. However, the use of HBIG is not currently recommended by the WHO and it is not feasible in most countries due to program logistics (lab-based screening to identify HBsAg-positive mothers, and due to the supply and cost of HBIG).

Recommendations TAG 2015

- **Vaccination and monitoring**

1. PAHO and countries should evaluate the current status of hepatitis B control and the feasibility of hepatitis B elimination, so that TAG can assess their progress and the feasibility of eliminating hepatitis B at the regional level.
2. TAG reminds countries to introduce the birth dose of the hepatitis B vaccine, i.e., the first dose within 24 hours after birth, in countries that have not already introduced it.
3. Countries should monitor the administration of the birth dose within 24 hours of birth.
4. Countries should document prevalence of hepatitis B infection among pregnant women and strengthen hepatitis surveillance.
5. TAG reiterates previous recommendations on hepatitis B vaccination for children, healthcare workers, and other high-risk groups.

Follow-up to 2015 TAG Recommendations

Continuing the inter-programmatic approach, several regional programs have included the elimination of Hepatitis as a public health problem by 2030, *including the EMTCT of HBV infection, which is considered a milestone on the road to HBV elimination*:

- PAHO Regional Plan on Viral Hepatitis (2016-2019) presented to the Directing Council in September 2015.
- PAHO Regional Immunization Action Plan (2016-2012) presented to the Directing Council in September 2015.

Other activities:

The PAHO Hepatitis Technical Advisory Committee (TAC) was established in November 2015 and a PAHO Core Group on Hepatitis was established in December 2015.

- During March 2016, a PAHO concept note for the Elimination of Perinatal Hepatitis B in the Americas was circulated among TAC members and various stakeholders.
- PAHO also elaborated a model for the feasibility of the perinatal elimination of Hepatitis B, which was presented at the experts' consultation during May 9-10, 2016.
- PAHO has also developed a field guide for Maternal and Neonatal Immunization that includes guidance on newborns and the Hepatitis B vaccine (vaccination during the first 24 hours of life).

Next steps:

Inclusion of eliminating the perinatal transmission of HBV infection in different PAHO regional initiatives such as:

- Elimination of the perinatal transmission of HBV infection through the EMTCT+ platform, to be presented to PAHO's Directing Council in September 2016 as part of the 2016-2021 Regional Plan for HIV and STI
- Inclusion of the progress of the elimination of perinatal transmission in the Regional Immunization Action Plan (2017-2022), to be presented to PAHO's Directing Council in 2017.
- In other maternal and child health regional plans initiatives, if foreseen.

Recommendations

- The TAG supports that the PAHO Directing Council formally sets a goal for the elimination of MTCT of Hepatitis B by 2020.
- The TAG assesses that EMTCT of Hepatitis B is feasible in the Americas by ensuring vaccination coverage equal or greater than 95% with one dose of Hepatitis B vaccine among all newborn babies within 24 hours of birth and with the third dose of Hepatitis B among children <1 year, respectively.
- The TAG reaffirms the recommendations on Hepatitis B vaccination made at the meeting in 2015 and notes the progress made towards the evaluation of the feasibility of Hepatitis B elimination.
- The TAG recommends that PAHO provides support to those countries of Central America and the Caribbean with the highest prevalence of HBsAg to achieve the elimination goal. PAHO should also establish a comprehensive plan, including strengthened surveillance and targeted surveys for all countries, with a special focus on those countries in Central America and the Caribbean with highest prevalence of HBsAg.
- The TAG recommends that measures to eliminate MTCT of Hepatitis B be integrated with efforts to eliminate MTCT of HIV and congenital syphilis and with other maternal, neonatal and infant health initiatives.

Extra Agenda Topics

Terms of Reference for the TAG

- Regional TAG Meetings will be held every two years.
- Sub-regional meetings will be held on alternate years. TAG members will be invited to participate based on availability, interest or expertise.
- There will be virtual TAG meetings held for urgent issues.
- Revised Terms of Reference for TAG Members will be circulated. They are now aligned with the SAGE's Terms of Reference.

Yellow Fever

At the request of the TAG Chair, a short briefing was given on the current global situation on yellow fever:

1. Global Epidemiological Situation

There are several ongoing yellow fever outbreaks in the AFRO Region. As of May 11 2016, Angola has reported 2267 suspected cases and 293 deaths. Of these, 696 have been confirmed by laboratory. Three countries have reported importations stemming from this outbreak, including the Democratic Republic of Congo (39 cases plus two autochthonous cases), the People's Republic of China (11 cases) and Kenya (two cases). Additionally, 51 suspected cases have been reported in Uganda, including seven that were laboratory confirmed.

2. Epidemiological Situation in the Americas

Epizootics due to yellow fever have been reported in Brazil, Peru and Ecuador. One human case has been reported in the municipality of Bady Bassit (Sao Paulo) 400 kilometers from the urban center of Sao Paulo, Brazil. This case is most likely a case of a jungle yellow fever, as this municipality is included in a risk area for the disease and vaccination is recommended for all residents of the zone. The vaccination status of this case, however, is unknown.

On April 22, PAHO issued an Epidemiological Alert in light of the circulation of yellow fever in the Region and in consideration of the current global situation. In this alert, PAHO advised Member States to maintain their capacity to detect and confirm cases of yellow fever, provide updated information for health professionals and training to allow them to properly detect and manage cases. PAHO also encouraged countries to maintain high vaccination coverage among at-risk populations.

3. Yellow Fever Vaccination Coverage in the Americas

Vaccine coverage in the Region among children at one year of age is around 70%. This coverage has been negatively affected by the current global vaccine shortage. Countries

are receiving around 50% of their estimated vaccine requirements. PAHO is therefore encouraging countries to build up national vaccine stockpiles in order to respond to potential outbreaks.

4. Communication from PAHO's Director

In light of the above facts, on 13 May 2016, PAHO's Director sent a letter to all ministries of health, updating them on this critical situation and reinforcing the current recommendations, especially given the close commercial relationship between Angola and Brazil, the possible risk of yellow fever case importation and the risk of the re-urbanization of this disease in the Americas.

**WHO South East Asia Regional - Immunization
Technical Advisory Group (SEAR-ITAG)**

**Report of the Seventh Meeting
SEAR-ITAG**

New Delhi, India, 7 to 10 June 2016



**World Health
Organization**

Regional Office for South-East Asia

Table of contents

Contents	Page
Table of contents	ii
Acronyms	iii
Introduction	1
Objectives	2
Conclusions and Recommendations	3
National Immunization Technical Advisory Groups (NITAGs)	3
SEAR Vaccine Action Plan	3
Equity	4
Immunization Legislation	4
Immunization Financing	5
Polio Eradication	7
Hepatitis B	9
Maternal and Neonatal Tetanus Elimination (MNTE)	10
Measles Elimination and Rubella/CRS Control	12
Data Quality	14
Vaccine Quality and Management	15
Adverse Events Following Immunization (AEFI)	16
New and Underutilized Vaccines Introduction (NUVI)	17
Way Forward	18
Annex 1: MEETING AGENDA	19
Annex 2: LIST OF PARTICIPANTS	

Annexes have been removed from the version included in the Yellow Book. The full meeting report is available on the SAGE website

ACRONYMS

AEFI	adverse events following immunization
AFP	acute flaccid paralysis
AI	appreciative inquiry
ATAP	access to affordable pricing
bOPV	Bivalent Oral Polio Vaccine
CTC	controlled temperature chain
FDA	Food and Drug Administration
GAP	Global Action Plan
GHSS	Global Health Sector Strategy
GPEI	Global Polio Eradication Initiative
GRISP	Global Routine Immunization Strategies and Practices
GVAP	Global Vaccine Action Plan
HBR	home-based records
IEC	Information Education and Communication
IPV	inactivated polio virus
ITAG	Immunization Technical Advisory Group
JRF	Joint Reporting Form
LB	live births
MNCH	Maternal, New-born and Child Health
MNTE	Maternal and Neonatal Tetanus Elimination
MOV	missed opportunities for vaccination
MRCV	measles and rubella containing vaccine
MRCV2	two-dose measles and rubella containing vaccine
NITAG	National Immunization Technical Advisory Group
NRA	National Regulatory Authority
NUVI	New and Under-utilized Vaccines
OPV	Oral Polio Vaccine
OPV3	three-dose Oral Polio Vaccine
PCV	pneumococcal conjugate vaccine
PQ	pre-qualified
RCCPE	Regional Commission for the Certification of Poliomyelitis Eradication
RI	routine immunization
RVAP	Regional Vaccine Action Plan
RVC	South-East Asia Regional Verification Commission for Measles Elimination and Rubella/CRS Control
SAGE	Strategic Advisory Group of Experts on Immunization
SDG	Sustainable Development Goals
SEAR	South-East Asia Region
SFI	sustainable immunization financing
SIA	supplementary immunization activity
SOP	standard operating procedures
tOPV	Trivalent Oral Polio Vaccine
VAP	Vaccine Action Plan
VDPV	vaccine derived polio virus
VPD	vaccine-preventable disease
WPV	wild polio virus

INTRODUCTION

The Seventh Meeting of the World Health Organization's South-East Asia Regional Immunization Technical Advisory Group (SEAR-ITAG) was held from 7 to 10 June 2016 in New Delhi, India.

The SEAR-ITAG is a regional technical expert group, established by the Regional Director of WHO's South-East Asia Regional Office, for providing advice on all aspects of prevention, control, elimination and eradication of vaccine-preventable diseases (VPDs). It comprises experts from disciplines such as programme management, communicable disease/vaccine-preventable disease control, virology, epidemiology and immunization. It meets annually with the participation of national expanded programme on immunization (EPI) managers, national surveillance focal points and partners, to review progress on increasing and sustaining immunization coverage, surveillance performance, programme issues, and matters related to vaccine quality and safety. It provides guidance to Member States on ways to improve and sustain overall high-quality performance in implementing immunization programmes.

The terms of reference of ITAG are as follows:

- Review Regional and Member State policies, strategies and plans for the control, elimination and/or eradication of vaccine-preventable diseases, especially for polio eradication, measles elimination, rubella/congenital rubella syndrome (CRS) control, and maternal and neonatal tetanus elimination (MNTE).
- Provide guidance on setting of regional priorities for immunization and vaccines.
- Make recommendations on the framework for development of national immunization policies as well as operational aspects of their implementation; and provide framework and approaches to periodic evaluation and strengthening of routine immunization services and systems.
- Advise Member States on appropriate choices of new vaccines and recommend optimal strategies for their introduction, including technical guidance for monitoring and impact evaluation of new vaccines once they are introduced into national immunization programmes.
- Promote and provide technical guidance for the implementation of high-quality vaccine-preventable disease surveillance, including laboratory networks for surveillance.
- Advise Member States on regulatory requirements to ensure quality and safety of vaccines used in national immunization programmes.
- Provide guidance on public private partnerships.
- Identify and advise on appropriate implementation research topics in immunization and vaccines, and review the conduct and results of such research projects.

The Meeting was chaired by Professor Gagandeep Kang. Other ITAG members present were Dr Robert Linkins, Professor Sanath Lamabadusuriya, Dr Charung Muangchana, Dr Yasho Vardhan Pradhan, Professor Mohammed Shahidullah and Professor Saw Win.

Other participants included:

- representatives from National Immunization Technical Advisory Groups (NITAGs) of Member States;
- members of the Strategic Advisory Group of Experts (SAGE) representing the Region;
- national EPI programme managers and surveillance focal points from 11 countries;
- immunization focal points from the South-East Asia Regional Office (SEARO) and WHO country offices;
- representatives from WHO headquarters;
- representatives from the United Nations Children's Fund (UNICEF); and
- local and global partners and stakeholders.

OBJECTIVES

Immunization activities involve multiple stakeholders at global, regional and country levels. There is an increasing and constant need for ensuring coordination, communication and coherence between all agencies involved in the funding, implementing, regulating and developing of immunization programmes and policies. Additionally, there are time-bound immunization and disease eradication/elimination/control targets, which attract intense scrutiny of stakeholders. Thus it is essential to have regular oversight and monitoring by a regional advisory body, and to have periodic course correction. In this Region, the annual SEAR-ITAG Meeting is the mechanism that supports this role.

The primary objectives of this meeting were as follows:

1. To review the performance status of national EPI programmes in relation to disease eradication/elimination/control targets; and review the implementation of recommendations of the Sixth SEAR-ITAG Meeting 2015.
2. To seek the guidance of SEAR-ITAG in effectively addressing the following priority areas:
 - implementation of the Global Vaccine Action Plan (GVAP);
 - mid-term review of the regional flagship programme of measles elimination and rubella/CRS control by 2020;
 - implementation of the Polio Eradication and Endgame Strategic Plan 2013–2018 (outbreak response preparedness, validation of the switch from tOPV to bOPV, IPV introduction, containment of polioviruses as per Global Action Plan III and legacy planning in SEAR countries);
 - validation of MNTE during 2016;
 - vaccine quality and management;
 - introduction of new and underutilized vaccines and health system strengthening for immunization outcomes.

CONCLUSIONS AND RECOMMENDATIONS

a. National Immunization Technical Advisory Groups (NITAGs)

While emphasizing that NITAGs are independent committees whose mandate is to advise their governments towards making evidence-based immunization policy decisions, ITAG commends SEAR Member States for integrating NITAGs into the immunization-related policy-making systems in their respective countries. ITAG also congratulates Member States on establishing NITAGs in all 11 Member States.

ITAG is of the opinion that the establishment of the SEAR-NITAG voluntary network in April 2016 is a significant step towards enhancing the capacity of NITAGs in the Region. ITAG in particular notes the remarkable contribution of NITAGs in reviewing implementation of the GVAP in their respective countries through National Immunization Programmes.

ITAG recommends that:

- a) The capacity of NITAGs to provide guidance on evidence-based approaches to strengthen immunization systems and services should be further enhanced by sharing country experiences, best practices and resources, as well as by peer-to-peer technical assistance through the 'SEAR-NITAG Network'. The technical agencies and development partners should ensure sufficient support for a functional secretariat for the Network.
- b) NITAGs now provide an annual report on their functioning to SEARO through their respective governments and WHO country offices. The annual reports, made in accordance with the standardized reporting format, should be reviewed at the annual SEAR-ITAG meetings. Further, individual NITAGs may consider using the WHO Collaborating Centre tool for periodic evaluation of functionality.
- c) NITAGs should consider inviting representatives from their respective countries, who serve on the SAGE, SEAR-ITAG or other regional TAGs (e.g. Regional Commission for the Certification of Poliomyelitis Eradication (RCCPE) and South-East Asia Regional Verification Commission for Measles Elimination and Rubella/CRS Control (RVC) to participate in their meetings.
- d) The role of NITAGs should not be limited to the consideration of recommendations for the introduction of new vaccines, but should extend to devising strategies for optimizing the use of existing vaccines and strengthening national immunization programmes.

b. South-East Asia Regional Vaccine Action Plan (SEAR-VAP)

ITAG congratulates WHO-SEARO on drafting the SEAR-VAP (2016–2020) in alignment with the goals of the GVAP (2011–2020) to reflect the joint commitment of Member States and other stakeholders towards achieving long-term collective goals in immunization in the SEA Region. ITAG recognizes the importance of defining goals, targets and priority areas for action in the SEAR-VAP, in the context of specific needs and challenges of Member States. ITAG opines that NITAGs should annually monitor and evaluate the achievement of set targets in accordance with the indicators defined by the SEAR-VAP framework.

ITAG recommends that all Member States:

- a) Develop annual plans for immunization consistent with the GVAP/SEAR-VAP.
- b) Establish a process to annually monitor the progress of SEAR-VAP implementation by an independent body such as their NITAG, and submit an annual progress report to the SEAR-ITAG through SEARO.

c. Equity

ITAG reiterates that equity in immunization is vital to ensuring benefits to all. ITAG believes that it is important to have country and region-specific policies/strategies in place to achieve equity in immunization. It notes the importance of improving access to marginalized populations where disease burdens tend to be disproportionately concentrated. ITAG invites Member States to focus on reaching these communities to achieve a higher degree of equity in immunization in the Region. As a means of operationalizing the outreach to these communities, ITAG recognizes the value of disaggregating data by geography, wealth and gender, generating such data where not available and streamlining specific strategies for prioritization of high-risk populations for interventions.

ITAG recommends that all Member States:

- a) Endorse lessons learnt from country experiences and promote equity in its different forms, including gender, sociocultural situation and geography.
- b) Must address the problem of under-immunized/unreached children and missed opportunities for vaccination (MOV) in order to achieve the GVAP goals.
- c) Should prioritize targeted interventions to administrative areas with high numbers of under-immunized/un-immunized children for increasing and sustaining population immunity most efficiently.

d. Immunization Legislation

ITAG is of the opinion that Immunization Legislation is an important milestone for Member States in protecting children's rights to quality immunization, and that it reflects a country's political commitment to the programmatic and financial sustenance of its National Immunization Programme.

ITAG recommends that all Member States:

- a) Recognize that the benefits of legislation, such as the Immunization Act of Nepal 2016, are core to achieving public health goals.
- b) Consider how such legislation may be advantageous to strengthening their immunization programmes.

e. Immunization financing

ITAG is encouraged to note that Member States continuously strive to introduce new and under-utilized vaccines and new technologies, while at the same time working towards achieving high and equitable immunization coverage by intensifying routine immunization and strengthening health systems. ITAG is aware that these efforts often increase the costs of national immunization programmes beyond the currently available allocations for immunization in their national budgets. It also notes the challenges posed by the differing wealth status of Member States (as reflected in the World Bank income categorization), and also by different phases of transition from Gavi support. Therefore, ITAG considers that addressing emerging needs for sustainable and predictable funding for national immunization programmes is a priority for the SEA Region.

ITAG recommends that all Member States:

- a) Develop a comprehensive and sustainable immunization financing plan as part of their national immunization or any equivalent plan. These plans should be updated periodically to ensure predictable financing for:
 - i. routine immunization to increase and sustain equitable immunization coverage;
 - ii. introducing new and under-utilized vaccines (NUV) based on available evidence;
 - iii. use of innovative technologies and strategies to promote immunization; and
 - iv. strengthening health systems for immunization outcomes.

f. Polio Eradication

ITAG congratulates Member States on maintaining polio-free status of the Region for more than 5 years since the last case due to wild poliovirus (WPV) was detected in January 2011. However, it notes with concern the detection of vaccine-derived polioviruses (VDPV) from stool specimens of Acute Flaccid Paralysis (AFP) cases, as well as from sewage samples in India during the last 18 months; also an outbreak of circulating vaccine-derived poliovirus type 2 (cVDPV2) in Myanmar in 2015.

ITAG congratulates Myanmar on strong measures taken by the Ministry of Health in response to the outbreak, but remains concerned at gaps in AFP surveillance, especially in the outbreak area. It notes that the outbreak response assessment team could not conclude with certainty whether transmission of the cVDPV2 had been interrupted. It recommends urgent measures to improve the quality of AFP surveillance and to initiate environmental surveillance.

ITAG recognizes the support and guidance of donors and partners in implementing the polio eradication and endgame strategy in the Region. It acknowledges the active oversight of the National Certification Committees for Polio Eradication (NCCPE) and the Regional Certification

Commission in maintaining surveillance standards, immunization and outbreak response preparedness.

ITAG notes the continued risk of WPV spread following an importation, as well as the ongoing risk of circulating VPDV due to OPV use. ITAG is concerned about the persistently low OPV3 coverage through routine immunization (RI) in India, Indonesia, Myanmar and Timor-Leste, and notes that SIA with tOPV had been conducted in each of these Member States prior to the switch from tOPV to bOPV, to mitigate the risks of VDPV2 emergence.

ITAG is also concerned about suboptimal AFP surveillance indicators in Indonesia, Myanmar, Sri Lanka, Thailand and Democratic People's Republic of Korea. ITAG notes the progress in expanding environmental surveillance in the Region, with the addition of sites in India and initiation of sites in Bangladesh and Indonesia. ITAG appreciates the performance of the laboratory network in support of AFP and environmental surveillance, but is concerned about performance issues in the Democratic People's Republic of Korea laboratory.

ITAG notes the Region's progress towards achieving the objectives of the 'Polio Eradication and Endgame Strategic Plan 2013–2018', including plans for IPV introduction. ITAG congratulates the ministries of health in all 11 countries for undertaking and validating the switch from tOPV to bOPV in April/May 2016 with support from WHO, UNICEF and other stakeholders. ITAG notes the challenges related to availability of sufficient IPV in the Region and measures taken to mitigate risks associated with short supply of IPV, such as the prioritization of IPV supplies to tier 1 and 2 countries. ITAG congratulates India for introducing off-label fractional dose IPV in eight states to stretch available IPV supplies. ITAG notes the progress in containment of all type 2 polioviruses as per Global Action Plan III (GAP III) in the Region despite the complexities involved in this area of work.

ITAG notes the efforts being made to ensure outbreak response preparedness in the Region, with special emphasis on preparedness for any type 2 poliovirus circulation in the post-switch period. It commends the authorization for use of mOPV2 and fractional dose IPV if an outbreak is detected.

ITAG appreciates initiation efforts in the Region to develop transition plans for polio assets in five priority countries – Bangladesh, India, Indonesia, Myanmar and Nepal – to ensure that these assets contribute to broader public health gains while sustaining polio-free status.

ITAG recommends that:

- a) All Member States should continue their efforts to achieve/sustain certification-level AFP surveillance.
- b) An urgent review of AFP surveillance indicators and processes at the national and subnational levels should be undertaken in Democratic People's Republic of Korea, Indonesia, Myanmar, Sri Lanka, Thailand and Timor-Leste. Corrective actions should be identified and immediately implemented.

- c) Environmental surveillance should be initiated immediately in Myanmar and in Nepal in 2016–2017. Thailand should also consider initiating environmental surveillance. Countries already conducting environmental surveillance should consider adding sites.
- d) India, Indonesia, Myanmar and Timor-Leste should continue to strengthen their routine immunization programmes through the development and implementation of programme improvement plans to maximize effectiveness of IPV administered as a part of routine immunization.
- e) Indonesia should ensure that IPV is introduced no later than July 2016.
- f) Global Polio Eradication Initiative (GPEI) partners should regularly share information on IPV supply with all Member States, including those that self-procure the vaccine.
- g) In view of the insufficient global IPV supply and the operational challenges associated with administering fractional dose of IPV, NITAGs should provide guidance to national programmes on IPV introduction strategies.
- h) All Member States should ensure that their outbreak response plans are in line with GPEI protocols for response to detection of type 2 poliovirus in the post-switch period, including authorizing the emergency use of mOPV2 and IPV.
- i) All Member States should ensure that containment activities are implemented as per Global Action Plan III (GAP III) within the stipulated timelines and in partnership with relevant stakeholders.
- j) Ministries of health in Bangladesh, India, Indonesia, Myanmar and Nepal should develop and finalize their transition plans for polio assets by end-2016.
- k) Certification activities should continue as per recommendations of the Regional Commission for Certification of Poliomyelitis Eradication (SEA-RCCPE).

g. Hepatitis B

ITAG notes the long history of immunization against hepatitis B in the SEA Region, and the achievements of Member States. However, it concludes that vaccination and control activities need to be accelerated in view of the estimated 100 million persons with chronic hepatitis B virus (HBV infection), resulting in an estimated 300 000 deaths a year from hepatocellular carcinoma (HCC), cirrhosis and other complications. HBV is highly transmissible, and newborn infants and children are at high risk. SAGE recommends two distinct but related public health interventions:

- administering a birth dose to prevent perinatal infection,
- followed by 2–3 subsequent doses giving complete protection to infants and young children.

ITAG notes the challenges of several Member States in providing timely birth-dose vaccination given the low rate of health-facility based deliveries or skilled birth attendance at home deliveries. However, the Region now has experience in overcoming this by successfully adopting innovative strategies, namely integration of birth dose with essential newborn care. While the birth dose is ideally administered within 24 hours, there are still protection benefits if given up to 7 days after birth.

ITAG considers the current global environment as very opportune for establishing a regional target for hepatitis B control through immunization, in keeping with the Global Health Sector Strategy (GHSS) for Viral Hepatitis 2016–2021 endorsed by World Health Assembly (WHA) 2016, the UN sustainable development goals (SDGs) and the GVAP. The GHSS aims at a 30% reduction of new cases of chronic viral hepatitis B by 2020, which is considered equivalent to 1% prevalence of hepatitis B virus surface antigen (HBsAg) among children.

The present environment also provides new opportunities for partner support at a stage where several Member States will be graduating from Gavi support. Experiences from other WHO regions have demonstrated how setting a control goal contributes towards heightened national commitment to hepatitis B control, and also indirectly focuses attention on strengthening routine immunization services. Furthermore, with many Member States currently developing polio legacy documents, it is an opportune time to transition polio assets and legacy to the control of hepatitis B in the Region.

ITAG recommends that Member States:

- a) Conduct a systematic review of hepatitis B vaccination coverage to identify gaps and causes of under-immunization – especially with regard to birth dose – and develop/implement strategies to bring coverage to target levels.
- b) Ensure that activities required for achieving hepatitis B immunization coverage goals are adequately reflected in national comprehensive multiyear plans (cMYPs) or other expanded programme on immunization (EPI) plans.
- c) As the overall control of viral hepatitis incorporates a range of strategies under the responsibility of different governmental units, it is critical that hepatitis B immunization strategies are clearly reflected in national action plans with clear delineation of responsibilities. NITAGs should advocate and oversee coordination between departments to achieve immunization goals.
- d) Closely coordinate with WHO and other technical partners to identify and address specific programmatic, implementation and monitoring challenges.

ITAG recommends that SEARO:

- a) Establishes a regional goal for control of hepatitis B as part of the Regional Vaccine Action Plan (RVAP). The control goal should be in alignment with the Global Health Sector Strategy on Viral Hepatitis and should have a target of $\leq 1\%$ HBsAg seroprevalence among children aged 5 years by the year 2020.
- b) Develops an action plan for accelerating hepatitis B immunization towards the regional control goal. Given the diversity of epidemiological situations, the plan must be guided by a comprehensive consultation process with Member States, relevant experts and partners, and based on country needs and resource requirements.

- c) Hepatitis B control action plan should be aligned with the RVAP, and consideration should also be given to the role of viral hepatitis A and E vaccination in a comprehensive hepatitis prevention strategy of national immunization programmes.

h. Maternal and Neonatal Tetanus Elimination (MNTE)

ITAG congratulates Indonesia on having achieved MNTE status as per WHO criteria in 2016, and the SEA Region on becoming the second of the six WHO regions after the European Region to achieve MNTE. ITAG considers Regional MNTE as another public health victory, proving that even access-constrained, remote and vulnerable high-risk populations can be reached.

However, sustaining MNTE requires vigilance. Member States that relied solely on routine service delivery or have reliable neonatal tetanus (NT) surveillance may face fewer challenges in sustaining MNTE as compared with Member States that employed SIAs in selected districts or in the country as a whole. Nevertheless, for all Member States, the post-elimination scenario requires addressing gaps related to access, coverage and quality of health care, and routinely reviewing district performance data. Negligence in this regard might well result in some districts, or the country as a whole, reverting to previous high MNT risk status.

As such, ITAG welcomes the WHO and UNICEF operational guidelines on *'Sustaining Maternal and Neonatal Tetanus Elimination (MNTE) once achieved by a country'* to serve as a basis for joint action between immunization programmes, Maternal and New-born Child Health (MNCH) and surveillance managers, to address gaps that could impact a Member State's ability to maintain MNTE.

ITAG recommends that Member States:

- a) that have achieved MNTE status since the year 2000 should periodically review the performance of each district as a joint exercise by the EPI, MNCH Programme, surveillance managers and partner representatives. The review should follow WHO and UNICEF operational guidelines on *'Sustaining Maternal and Neonatal Tetanus Elimination (MNTE) once achieved by a country'*. Member States should use the assessments to implement corrective measures, taking into account the country policy/strategy, local context and feasibility.
- b) that have achieved MNTE status before the year 2000 should improve and sustain sensitive neonatal tetanus (NT) surveillance in every district to maintain elimination status, as districts should remain at a reported/estimated annual NT rate below 1/1000 Live Births (LB).
- c) that have not yet optimized immunization schedules for tetanus toxoid vaccination should aim at optimizing them to ensure full and early protection against tetanus with booster doses for both genders during childhood and adolescence.

ITAG recommends that SEARO:

- a) develop an activity plan for monitoring/maintaining MNTE status in priority countries. This should include but not be limited to:
 - i. a standard set of data to be reported, analysed and reported back to Member States for action, and
 - ii. establishing a standardized format for MNTE assessment post-validation.
- b) support select countries in their district-level annual performance review.

i. Measles elimination and rubella/CRS control

ITAG is encouraged by Member States' commitment to the regional goal of measles elimination and rubella/CRS control by 2020. Nevertheless, ITAG believes that current efforts to close immunity gaps and strengthen case-based surveillance and reporting need to be intensified. To this end, ITAG will monitor a number of milestones to track progress of Member States towards reaching the measles elimination and rubella/CRS control goal by 2020.

ITAG commends Member States on progress made in providing MRCV1 and MRCV2 with high coverage through their respective routine immunization programmes. ITAG commends Member States on the formation of National Verification Committees, and SEARO on the formation of the Regional Verification Commission for Measles and Rubella. ITAG expressed concern over a resurgence of measles in Bhutan and an outbreak in Sri Lanka.

ITAG encourages exploring the option of utilizing the Region's polio infrastructure towards the control/elimination of measles and rubella/CRS as part of the polio legacy plan. ITAG acknowledges that high vaccination coverage may necessarily not indicate the case load or interruption of transmission in a population, and thus emphasized the need to look into surveillance performance as key indicators towards verification progress. The centrality of surveillance was underlined, based on the Region's experience with polio elimination, and thus it was emphasized that the Region should put in all resources to meet global standards of surveillance.

ITAG encourages Member States to report progress on measles elimination and rubella/CRS control to the Regional Verification Commission following review by their respective National Verification Committees.

ITAG acknowledges that the SEA Region has the world's largest birth cohort, and that measles elimination and rubella/CRS control activities will have far-reaching implications beyond the Region and towards global progress.

ITAG recommends that:

- a) All National Verification Committees (NVCs) should review and report progress on measles elimination and rubella/CRS control in their country to the Regional Verification Commission.

- b) The Regional Verification Commission Secretariat in WHO SEARO should present a report on progress made towards meeting the goal of measles elimination and rubella/CRS control at the next SEAR-ITAG meeting in 2017.
- c) For Member States that have introduced measles and rubella containing vaccine (MRCV), NITAGs should recommend that governments commit to rubella elimination by 2020 in keeping with the regional measles elimination goal. In Member States yet to introduce MRCV, namely India and Indonesia, efforts should continue to reach the regional rubella control goal. A 2020 target for regional rubella elimination should be set once all Member States have introduced MRCV.

ITAG recommendations related to closing the immunity gap:

- a) All Member States should determine immunity profiles by birth cohort for various age groups (through desk reviews, sero-surveys or other mechanisms) and develop/implement plans to fill any gaps, including use of available opportunities for immunization, optimization of immunization schedule or implementation of supplementary immunization activities (SIAs) when appropriate.
- b) All Member States should monitor two-dose measles and rubella containing vaccine (MRCV) coverage at subnational levels and implement corrective actions when needed, in line with Global Routine Immunization Strategies and Practices (GRISP).
- c) India should begin to implement national wide-age range campaigns using MRCV by the end of 2016. This should be followed immediately by the introduction of MRCV in the routine immunization schedule.
- d) Indonesia should begin to implement national wide-age range campaigns using MRCV by mid-2017. This should be followed immediately by the introduction of MRCV in the routine immunization schedule.
- e) Democratic People's Republic of Korea should introduce MRCV in the routine immunization schedule as soon as possible, preferably no later than 2017.
- f) All Member States should consider verification of measles and rubella immunity status during the school and college admission process, and also among other risk groups, and plan vaccination as necessary.
- g) All Member states should consider developing subnational measles elimination and rubella control/elimination workplans, such as those that have proved to be effective in the polio eradication programme.

ITAG recommendations related to MR surveillance:

- a) All Member States should conduct subnational risk assessments of measles and rubella transmission and implement risk reduction activities.
- b) All Member States should revise national measles and rubella surveillance guidelines in line with the updated regional surveillance guidelines and indicators.
- c) All Member States should strengthen laboratory-supported case-based surveillance for measles and rubella as per the Framework for Verification of Measles elimination and Rubella

control/elimination. India and Indonesia should continue to expand case-based surveillance following wide-age range campaigns.

- d) All Member States should include linked laboratory and epidemiologic case-based data in their national measles/rubella surveillance systems, and report these data to WHO on a weekly basis, in line with current reporting requirements.
- e) SEARO should update regional measles and rubella surveillance guidelines and indicators in line with the Global Framework, tailoring guidelines to account for countries at different stages of measles elimination and rubella control.
- f) SEARO should encourage operational research studies on alternative sample collection (for example, dried blood spots), new vaccine delivery technologies and point-of-care diagnostics, to support Member States such as Bhutan, Maldives, Myanmar and Nepal, where conditions are challenging.

ITAG recommendations related to the MR laboratory network:

- a) All laboratories in the Regional Measles and Rubella Network to institute a quality assurance process that includes routine internal auditing, and ensures an adequate supply of kits and reagents.
- b) All Member States to collect adequate specimens to characterize measles and rubella genotypes. Findings should be linked with epidemiological case-based data to identify chains of transmission. Findings should be regularly shared with all stakeholders.

Among Member States with established CRS surveillance, ITAG recommends that:

- a) Bangladesh and Nepal should conduct an evaluation of their CRS surveillance systems and present their findings at the next SEAR-ITAG meeting in 2017.
- b) All Member States conducting CRS surveillance to report their findings to WHO on core variables as per the data dictionary on a monthly basis, as well as through Joint Reporting Form (JRF) on an annual basis.

j. Data quality

ITAG recognizes that accurate data is the cornerstone for formulating evidence-based policy, providing operational support for immunization systems and also essential for accountability at all levels.

ITAG notes that high-quality data are crucial for monitoring progress towards achieving national, regional and global goals. ITAG noted that subnational immunization coverage was not available for some Member States, nor was there a mechanism to validate such data of Member States that did provide it. ITAG notes that demographic and GIS information need to be updated by a few Member States and that case-based data collection and reporting for other VPDs like NT, diphtheria and pertussis is yet to be initiated.

ITAG appreciates the detailed review of data conducted by SEAR-IVD during 2015–2016 on immunization system performance and VPD surveillance performance indicators that were reported through the annual joint reporting form (JRF), and provided feedback to Member States on data quality and data analysis. ITAG notes that JRF data are an important source of information and performance indicators, which are used for the monitoring and accountability framework of GVAP and reporting to SAGE and WHA.

SEAR-ITAG noted the emphasis laid by SAGE on accurate data regarding prevalence and/or incidence of vaccine-preventable diseases (VPDs) and immunization system performance for evidence-based policy and operational support. ITAG reaffirmed the position of SAGE that the improvement of data quality should be one of the highest priorities for all stakeholders in the early part of the Decade of Vaccines. Likewise, data quality improvement is a Strategic Focus Area in Gavi, The Vaccine Alliance's 2016–2020 strategy; thus, Gavi-eligible countries should meet this requirement.

ITAG recommends that Member States:

- a) Conduct annual reviews to assess data quality of immunization coverage and VPD surveillance using WHO assessment tools. In-country independent resources, such as academia and professional associations, may also be used to ensure the quality of the assessments.
- b) Develop, implement and monitor data quality improvement measures in response to the assessments, and develop surveillance data management systems to ensure that case-based data on Acute Flaccid Paralysis (AFP), Measles and Rubella and other priority vaccine-preventable diseases, are collected as per WHO protocols.
- c) Conduct periodic national and subnational surveys to validate immunization coverage data. India and Indonesia should conduct periodic estimations of immunization coverage first at the subnational level using the WHO/UNICEF methodology for estimation of coverage.
- d) Ensure that subnational level immunization coverage data are shared with SEARO.

ITAG recommends that SEARO provide technical support to Member States for:

- a) Analysing and interpreting immunization data, and using the findings to develop policies and data quality improvement measures.
- b) Developing data quality improvement plans and guidelines for assessing data quality.
- c) Reviewing, modifying and upgrading national AFP, Measles-Rubella and VPD surveillance and immunization information systems.

k. Vaccine quality and management

NRA strengthening

ITAG recognizes that the National Regulatory Authority (NRA) of Member States is responsible for the safety, quality and efficacy of medicines/vaccines regardless of the procurement policy, that is, irrespective of whether procurement is from pre-qualified (PQ) suppliers or is locally produced.

ITAG fully realizes that some NRAs in the Region have limited resources, and therefore reminded such NRAs to use measures such as using WHO pre-qualified vaccines, learning from the experience of other NRAs and working towards regulatory convergence/harmonization under internationally accepted guidelines.

Also, ITAG encourages promotion of synergies through reliance and networking among Member States in order to further strengthen the NRA capacity.

ITAG also noted WHO's role to regularly assess NRAs in the Region using standard WHO indicators to ensure that vaccines produced by regional manufacturers are considered for WHO pre-qualification.

ITAG reminded that the concept of functionality has now been replaced by a benchmarking approach that indicates a country NRA's 'maturity levels' rather than it being adjudged 'functional' or 'non-functional'.

Related to NRA strengthening, ITAG recommends

1. That Member States:

- a) ensure that National Regulatory Authorities (NRAs) actively participate in addressing regulatory issues related to the vaccine life-cycle (namely manufacturing, regulation, distribution) in the newly instituted SEAR regulatory network.
- b) ensure that NRAs in their respective countries enforce good distribution and storage practices, and monitor AEFI surveillance.
- c) Bangladesh finalizes the new drug policy and drug act to reinforce the importance of the NRA, assure adequate resources, and continue to invest significantly in the NRA.
- d) Myanmar reinforces the Food and Drug Administration (FDA) to become an independent NRA and continues to invest significantly in the NRA.

2. That SEARO:

- a) facilitates training on the new NRA assessment tool for all concerned national staff.
- b) supports the Region and Member States in implementing recommendations of the SEAR regulatory network.

- c) supports the NRA in Bangladesh to achieve a maturity level that is required for the vaccine manufacturers of the country to be eligible for WHO pre-qualification functions as early as possible.
- d) continues to support the Myanmar NRA in capacity-building.
- e) continues to encourage and facilitate inter-country cooperation as an effective means of optimizing existing capacity and building capacity at the same time.

Vaccine availability and quality

ITAG recognizes that there is a global need to expand the number of pre-qualified vaccine manufacturers to create a more stable and competitive market. ITAG appreciates the actions taken by all stakeholders to minimize stock-outs resulting from the global shortage of BCG vaccines in 2015 and to ensure availability of sufficient buffer stocks of BCG vaccines in 2016. ITAG also understands the multiple challenges in expanding the cold-chain capacity for vaccine storage in Member States and it reminds the Gavi-eligible countries to make use of Gavi's cold-chain optimization platform, where relevant to address this challenge. Furthermore, ITAG reiterates the importance of long-term cost-saving plans to help cold-chain expansion in view of planned new vaccine introductions in countries.

Related to vaccine availability and quality, ITAG recommends

1. That Member States:

- a) especially those with limited NRA capacity, continue to exclusively use WHO pre-qualified vaccines for their immunization programmes.
- b) enhance interactions between NIP managers and vaccine producers at all levels – national, regional and global – to provide manufacturers with accurate and timely information on vaccine demands and to address current vaccine shortages, especially for basic vaccines.
- c) explore mechanisms of cooperation, such as the ASEAN Initiative on Vaccine Security, to promote regional access to an assured quantity and quality of vaccines at an affordable price.

2. That SEARO:

- a) explore pathways to pre-qualify the cholera vaccine manufactured by Bangladesh.

I. Adverse Events Following Immunization (AEFI)

ITAG recognizes the importance of proactively engaging the media to overcome negative outfall in case of occurrence of serious AEFI. ITAG congratulates India on the initiative taken in terms of transparency and dissemination of information by publishing AEFI details on its Health Ministry's website and urges other Member States to take similar approaches. ITAG took note of described policies with regard to compensation/hospitalization expenses for AEFI cases. ITAG congratulated Sri Lanka on its intensified AEFI surveillance through tracking and post-mortems following reports

of AEFI related to pentavalent vaccines. ITAG took note of India's experience regarding its recently revised initiatives to improve AEFI surveillance.

Related to AEFI, ITAG recommends

1. That Member States:

- a) work with academic institutions/partners to build capacity to conduct causality assessments for AEFI surveillance.
- b) share AEFI data with vaccine manufacturers through the NRA and NIP to consolidate the safety profile of newly introduced vaccines.

2. That SEARO:

- a) continues to support AEFI committees in AEFI investigation activities, finalizes the manual for field investigation of AEFI and facilitates its implementation at the country level.

m. New and Underutilized Vaccines Introduction (NUVI)

Dengue vaccine

The ITAG took note of the progress made in the research and development of dengue vaccines. It further noted that the new WHO position paper endorsed by SAGE on dengue vaccines would be available in July 2016. However, ITAG reminded national immunization programmes and their partners that there would be many tasks to be accomplished as per SAGE recommendations, should Member States consider introducing the new dengue vaccine CYD-TDV.

ITAG recommendations related to dengue vaccine:

- a. Member States considering the use of currently available dengue vaccine should evaluate epidemiological data such as age-specific seroprevalence rates and/or age-specific incidence rates of disease.
- b. NITAG decisions with regard to introduction of the dengue vaccine should carefully consider country-level assessment, local priorities, national and subnational dengue epidemiology, predicted impact and cost-effectiveness with country-specific hospitalization rates and costs, affordability and budgetary impact.
- c. Dengue vaccine introduction should be part of a comprehensive dengue-control strategy that includes effective and sustained vector control, best evidence-based clinical care for patients and robust dengue surveillance.

Other NUVI

ITAG notes that Member States have achieved significant progress in introducing new vaccines in the SEA Region. ITAG especially noted that although Bangladesh introduced the inactivated polio vaccine (IPV) and pneumococcal conjugate vaccine (PCV) simultaneously, it has faced several programmatic challenges. Also noted was the progress in introduction of rotavirus vaccine in the Region, where Thailand has introduced rotavirus vaccine as a pilot project in a single province, while India has introduced an indigenously manufactured rotavirus vaccine in four States. ITAG also congratulated Indonesia and Myanmar for preparatory activities to introduce the JE vaccine in their national immunization programmes in 2017. ITAG requested all Member States to share locally generated information about immunogenicity, efficacy, the duration of protection, safety issues of new vaccines introduced and challenges encountered.

Related to other NUVI, ITAG recommends:

- a) Member States introducing multiple vaccines to children during a single visit should provide information, education and communication (IEC) to parents/guardians that in the event of non-availability of one (or more) vaccine(s) due to 'stock-out' or any other reason, the other available vaccine(s) should be given to the child at the prescribed time in the national schedule. The vaccine(s) that is/are missed should be administered when available.
- b) Member States to educate and train health staff in the value and safety of multiple vaccines administered in a single visit.

The way forward

ITAG requests WHO-SEARO and all concerned partners to work towards setting goals in accordance with the Recommendations set forth in this report. It also directs them to prepare a progress report to be presented at the next annual ITAG meeting. Key actions for WHO-SEARO will be to:

1. provide technical assistance to Member States and facilitate implementation of ITAG recommendations in the Region
2. closely monitor the status of implementation of recommendations of ITAG and support as per the needs of the Member States.
3. strengthen research and development in the Region to generate evidence related to progress towards vaccine-preventable diseases.
4. present the implementation status and progress of the Region to the ITAG chair and members in June 2017.

WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR THE WESTERN PACIFIC

ABBREVIATED MEETING REPORT

For the complete Meeting Report, please visit the WHO SAGE Website¹

**25th Meeting of the Technical Advisory Group on Immunization and Vaccine-
Preventable Diseases**

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¹ <http://www.who.int/immunization/policy/sage/en/>

NOTE

The views expressed in this report are those of the participants of the 25th Meeting of the Technical Advisory Group on Immunization and Vaccine-Preventable Diseases in the Western Pacific Region and do not necessarily reflect the policies of the conveners.

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DRAFT

This report has been prepared by the World Health Organization Regional Office for the Western Pacific for Member States in the Region and for those who participated in the 25th Meeting of the Technical Advisory Group on Immunization and Vaccine-Preventable Diseases in the Western Pacific Region in Manila, Philippines, from 26 to 29 July 2016.

1. SUMMARY

The Twenty-fifth Meeting of the Technical Advisory Group (TAG) on Immunization and Vaccine-Preventable Diseases in the Western Pacific Region was held from 26–29 July 2016 in Manila, Philippines. The meeting was attended by seven TAG members, six temporary advisers, 28 participants from 16 countries and areas, and 76 representatives from partner organizations, and WHO staff from headquarters, the Regional Office for the Western Pacific and country offices.

The meeting participants discussed progress towards achieving the targets and indicators for the polio endgame; elimination of measles, rubella, and maternal and neonatal tetanus (MNT); and accelerated control of hepatitis B and Japanese encephalitis (JE). Discussions also covered evidence-based introduction of new vaccines and decision making processes, as well as vaccine safety and regulatory capacity. The regional immunization coverage goals aim to ensure equity and sustainability in immunization services to reach underserved populations and improve data quality.

TAG's key recommendations included setting a regional rubella elimination target date of 2020; and finalizing the *Regional Strategies and Plan of Action* on measles and rubella. Member States were recommended to prioritize available stocks of inactivated poliovirus vaccine (IPV) for high risk areas and to explore the programmatic feasibility of using a fractional dose via intra-dermal administration. The TAG recommended the use of a JE incidence target of < 0.5 cases per 100 000 population in the targeted population (typically children aged <15 years) in affected areas. The TAG reiterated the importance of establishing a second year of life platform for immunization as an opportunity to reach all children. Member States were encouraged to work with WHO and partners to ensure vaccine security and avoid stock-outs through regular vaccine forecasting, timely procurement and adequate resource allocation, making use of the Middle Income Country strategies and the Vaccine Product, Price and Procurement (VP3) platform to overcome potential risks to vaccine security. Member States and the Region were encouraged to take a cautious approach when considering the use of dengue vaccine, closely following advice in the current position paper and any additional recommendations from Strategic Advisory Group of Experts (SAGE).

2. CONCLUSIONS AND RECOMMENDATIONS

2.1.1. Sustaining polio-free status and implementation of polio endgame strategies

1. Sustaining polio-free status and implementation of polio endgame strategies

1. The TAG acknowledges the progress in implementing the global *Polio Eradication and Endgame Strategic Plan 2013–2018*. The TAG congratulates the 16 countries still using oral poliovirus vaccine (OPV) in 2016 on their successful switch from trivalent OPV to bivalent OPV, as well as the three countries and areas that transitioned to an inactivated poliovirus vaccine (IPV)-only schedule in 2015.
2. The TAG notes with disappointment and concern the global supply shortages that have led to significant delay in IPV introduction in Mongolia and Viet Nam, the insufficient IPV supply currently reported in China, Papua New Guinea and Philippines, and the anticipated stock-outs expected in eight Pacific island countries. The TAG reaffirms the key role of IPV in priming populations in case of emergence of vaccine-derived polioviruses type 2 and to a lesser degree in decreasing the potential occurrence of type 2 outbreaks in the post-switch period.
3. The TAG notes the need for development and implementation of strategies to provide protection against type 2 poliovirus to populations unprotected due to delayed introduction or stock-out of IPV, including vaccine dose-sparing and priority allocation to higher risk districts/provinces in order. The TAG commends China for its efforts in accelerating its production of IPV in order to respond to anticipated supply shortfalls in 2017.
4. The TAG notes that, in 2015, two countries (Papua New Guinea and the Philippines) were identified as being at high risk for ongoing poliovirus transmission following importation.
5. Coverage with three doses of polio vaccine at the national level is high in the Region (90% or more); however, there are still countries or areas not achieving this level. The TAG notes the high quality of surveillance for acute flaccid paralysis cases at the regional level, but surveillance performance varies among the countries and areas. These factors, in combination with reports of periodic vaccine stock-outs, highlight the importance of all countries and areas to remain vigilant and to sustain high performance in poliovirus surveillance indicators.
6. The TAG commends the quick and comprehensive response by the Lao People's Democratic Republic to the circulating vaccine-derived poliovirus (cVDPV) type 1 outbreak leading to interruption of virus transmission within 120 days.
7. The TAG urges countries and areas to refer to the revised polio outbreak response protocol and the monovalent OPV (mOPV) type 2 management and removal procedures as guiding documents.
8. The TAG notes the need to ensure the presence of national mechanisms to facilitate expedited importation and use of mOPV type 2 in case of a polio type 2 event/outbreak.
9. The TAG acknowledges the plan for the Global Polio Laboratory Network (GPLN) to expand the number of laboratories in the Region with the capacity to perform intratypic differentiation and to introduce an optimized intratypic differentiation method to increase the sensitivity for detecting and identifying polioviruses quickly.
10. The TAG notes that four countries in the Region (Australia, China, Japan and Malaysia) are performing environmental surveillance and recognizes efforts to establish environmental surveillance in the Philippines in 2016.

11. The TAG is pleased to note that by the end of 2015 all countries in the Region have nominated national polio containment coordinators.
12. The TAG notes the need to support implementation of Phase I (second part) of the third *WHO global action plan to minimize facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of routine OPV use (GAPIII)* for preparation for containment of Sabin/OPV poliovirus type 2 by 31 December 2016.

2.1.2. Hepatitis B accelerated control

The TAG is pleased that the ambitious regional goal of reducing hepatitis B seroprevalence among 5-year-old children to less than 1% by 2017 has been achieved, notably ahead of schedule in many Member States. While the TAG celebrates the impressive success in reducing hepatitis B prevalence to less than 1% among immunized cohorts within the Region, the TAG encourages continued commitment to assure that all countries within the Region reach this 1% goal and recognize the importance of developing post-2017 regional goals. The TAG endorses the 2016 recommendations of the hepatitis B Expert Resource Panel (ERP), noting it is important that ministries of health encourage the delivery of babies in health facilities, help strengthen the coordination between the Expanded Programme on Immunization (EPI) and Maternal and Child Health (MCH) for timely administration of hepatitis B birth dose and ensure effective monitoring and reporting of birth-dose coverage.

2.1.3. Japanese encephalitis (JE) accelerated control

The TAG notes several important advances in JE control during the past year. In March 2016, the JE Expert Resource Consultation (ERC) convened and proposed strategies and targets to achieve the regional goal for accelerated control of JE. These strategies, targets and timelines, together with advances in vaccines and new WHO guidance and programmatic steps by Member States promise to move the Region towards achievement of the regional goal. Two countries took significant steps in increasing JE vaccine coverage: the Lao People's Democratic Republic successfully introduced JE vaccine nationally in 2015 following completion of the final phase of a nationwide catch-up campaign earlier in the year; and Cambodia conducted a successful national JE catch-up campaign in March 2016 and has initiated national introduction of routine JE vaccination. In addition, Viet Nam successfully applied for Gavi funds in September 2015 and will soon begin a JE vaccination campaign to enhance the national JE vaccine programme.

Although some progress has been made, weaknesses in surveillance systems continue to limit efforts to estimate disease burden, define target populations for vaccination, and measure the impact of vaccination in some countries. Strengthening of surveillance in countries that have not yet achieved a high degree of JE control is critical for providing disease burden data and evidence of vaccine impact.

2.1.4. Measles and rubella elimination

1. The TAG notes that endemic measles transmission is ongoing in several countries, particularly countries with large populations, but the regional incidence of measles has decreased in the last 18 months since 2014. In March 2014, the Regional Verification Commission for Measles Elimination in the Western Pacific verified measles elimination to have been achieved and sustained in Australia, Macao SAR (China), Mongolia, and the Republic of Korea, and in March 2015, in Brunei Darussalam, Cambodia and Japan. Some of these countries are repeatedly exposed to imported measles virus from countries with endemic virus transmission. From 2015 to 2016, measles virus transmission was re-established in Mongolia following the largest measles outbreak in the country for the last 30 years.

2. Due to active implementation by Member States of strategies and activities proposed by the *Western Pacific Regional Plan of Action for Measles Elimination* from 2003 to 2012, the Region experienced dramatic declines in measles incidence. However, the recent resurgence of measles in endemic countries or large-scale measles outbreaks following importation has revealed that the susceptible population is largely comprised of infants too young and adolescents/adults not regularly reached by current immunization strategies. The TAG recalls that the 54th session of the WHO Regional Committee for the Western Pacific urged Member States to offer all children two doses of measles vaccine to achieve 95% population immunity in each birth cohort in every district in 2003.
3. The TAG notes that many countries in the Region have been utilizing the measles elimination platform and strategies to initiate or accelerate activities for rubella elimination. Several countries in the Region have made significant progress towards rubella elimination and aim to eliminate rubella by 2020.
4. The TAG acknowledges that WHO has prepared a draft *Measles and Rubella Elimination in the Western Pacific - Regional Strategies and Plan of Action* in consultation with national immunization programmes of Member States and partners.
5. The TAG notes the substantial progress towards rubella elimination in the Region; in particular, China has steadily reduced rubella incidence since 2008 to record low levels of 0.6 cases per 100 000 population in 2015 and documented a decrease in endemic genotypes from at least four to two genotypes in 2015, reflecting increasing pressure on rubella virus to maintain its reservoir.

2.1.5. Maternal and neonatal tetanus elimination

1. The TAG congratulates Cambodia on the 2015 achievement of validation of maternal and neonatal tetanus elimination (MNTE).
2. The TAG also commends the Philippines on the 2015 achievement of validation in 16 of 17 regions and progress towards national validation.
3. The TAG notes the low proportion of the regional population that routinely receives booster vaccination against diphtheria after the age of 6 years.

2.1.6. Strengthening routine immunization systems-equity and sustainability

1. The TAG acknowledges the efforts the Member States are making in reducing immunization disparities and filling gaps in vaccinations and immunization services, particularly among underserved populations.
2. The TAG notes the uneven progress in vaccination coverage at subnational levels that may be related to uneven immunization service provision, mobile populations, vaccine hesitancy, and other factors in low- and middle-income countries. These coverage disparities can negatively impact efforts to achieve elimination and control of vaccine-preventable diseases and pose a risk of resurgence of diseases.
3. The TAG acknowledges WHO and partners' efforts to address vaccine security through strengthening effective vaccine management and financial sustainability in low- and middle-income countries.
4. The TAG takes note that vaccine stock-outs at both national and subnational levels were reported in countries and caused some interruption of immunization services. Some of these stock-outs were due to internal planning and distribution issues, while others were due to vaccine shortages in the international market.

5. The TAG acknowledges the efforts the Regional Office and the Member States are making to sustain achievements that have been made in immunization.
6. The TAG takes note of the potential risk of vaccine hesitancy and therefore the benefits of active stakeholders' and community participation in reducing vaccine hesitancy.
7. The TAG notes the important role and responsibilities of private providers in achieving the goals of the Global Vaccine Action Plan (GVAP) and the *Regional Framework for Implementation of the Global Vaccine Action Plan in the Western Pacific* and recognized synergy between public and private partnership in order to strengthen immunization services.

2.1.7. Strengthening evidence-based immunization decision-making

1. The TAG acknowledges the continuing need for strengthening of national evidence-informed immunization decision-making processes due to the introduction of many new vaccines, increasing programme costs, competing public health priorities, and an increasing demand for transparency from communities.
2. The TAG acknowledges the efforts made by Member States, the Regional Office and partners towards improving immunization policy-making processes throughout the Region.
3. The TAG notes that sound and credible evidence-based decision-making methods and processes are needed. This may occur through a national immunization technical advisory group (NITAG) or equivalent body. The TAG acknowledges that the term NITAG may not be the ideal description for every context; in absence of an appropriate alternative, the term 'NITAG or equivalent' is proposed to be used for the time being.
4. The TAG notes that the Region still has much progress to make to achieve the target of having a functional NITAG or equivalent in every country by 2020; some countries have yet to form a NITAG or equivalent, and existing NITAGs have varying levels of functionality.
5. The TAG notes that an evaluation tool for NITAGs or their equivalents has been developed and is available on the NITAG Resource Centre. This tool may aid Member States with improving their immunization decision-making processes.
6. The TAG notes the particular challenges of ensuring sound evidence-informed decision-making in the Pacific island countries and in the feasibility of establishing NITAGs in all countries due to limited human and financial resources and expertise.
7. The TAG notes that many of the challenges faced by NITAGs are common throughout the Region and may be addressed through cross-collaboration among NITAGs.

2.1.8. Strengthening routine immunization – Data quality

1. The TAG acknowledges that the quality of regional-level data to monitor progress towards GVAP and Regional Framework goals is affected by incomplete and delayed submission of the WHO-UNICEF Joint Reporting Form (JRF), and poor response rate to queries addressing inaccurate or missing information in the JRF. Completeness of information is critically low for financing indicators, and very few countries are sharing information on vaccine pricing and procurement mechanisms.
2. The TAG acknowledges that national immunization coverage monitoring is inconsistent across different sources, and data quality issues are affecting both numerators and denominators, in some countries to a degree that affects profoundly the usability of routine administrative data. High-quality coverage surveys could be useful in validating

national routine coverage monitoring and quantitatively supporting key factors for EPI programme management.

3. The TAG notes that there are newer tools and approaches that could be used to assess the quality of national data and to support development of a specific data improvement plan.
4. The TAG notes that digitization of aggregated or individual case-based information within EPI represents an opportunity to strengthen data management and quality on coverage monitoring; however, it requires close coordination between EPI and other government stakeholders.

2.1.9. Strengthening vaccine safety surveillance and regulatory capacity

1. The TAG reiterates that ensuring vaccine/immunization safety and effectively responding to immunization safety incidents are critical to build and maintain public trust in national EPI programmes.
2. The TAG notes that Member States have worked strenuously on analysing the capacity gap, developing regional and national guidelines on causality assessment and communications, and providing national and subnational trainings in Cambodia, the Lao People's Democratic Republic and Viet Nam.
3. The TAG notes that strengthening the surveillance system of adverse events following immunization (AEFI) is necessary, particularly in middle-income countries. Reporting rates of AEFI are significantly improved, and as of 2015, 17 countries are maintaining higher reporting rates compared with the WHO-standard AEFI reporting rate of 10 AEFI cases per 100 000 surviving infants.
4. The TAG notes that the Regional Office and Member States have made an effort to continue periodic effective vaccine management assessments and implement activities in the improvement plan in Cambodia, Kiribati, Mongolia and Viet Nam.
5. The TAG notes that the National Regulatory Authority (NRA) system for vaccines and medicines was assessed in Cambodia, the Lao People's Democratic Republic and Mongolia in 2015-2016.
6. The TAG notes that the WHO Regional Office and Member States made progress with strategic planning and risk communication at its fourth workshop.
7. The TAG notes the ongoing important collaboration between WHO/EPI and WHO/Essential Medicines and Technology on effective vaccine management activities.

2.1.10. Evidence-based introduction of new vaccines

The TAG notes that low- and middle-income countries in the Western Pacific Region have made significant progress in introducing new and underutilized vaccines, yet still lag behind high-income countries in including new vaccines in their national immunization programmes. In addition, upper-middle-income countries lag behind low- and lower-middle-income countries in including some new vaccines in their national immunization programmes, in part because they do not have access to support from donor organizations for introductions that low- and lower-middle-income countries have. Achievement of the Decade of Vaccines goal for introduction of new and improved vaccines requires that countries evaluate evidence on disease burden including surveillance, cost, the role of other disease prevention and control measures, vaccine characteristics, vaccine supply, and immunization programme and health system strength. An increasing number of Member States are collecting and evaluating such evidence to develop and sustain vaccine introduction policies, and some Member States have consolidated the evidence in national plans. WHO plays an important role in providing technical support and capacity-building for the collection of such evidence. Surveillance with

laboratory confirmation is a key source of evidence, and the quality of surveillance requires consistent attention.

2.1.11. Dengue

1. The TAG notes with interest the publication of a WHO position paper on dengue vaccine on 29 July 2016, after registration of a vaccine in several countries. The TAG also notes the participation of investigators from several Western Pacific Region countries in clinical trials conducted by vaccine manufacturers of this vaccine. The TAG notes that there are also three candidate dengue vaccines under development which may be available in the next few years. The TAG notes that the registered vaccine is undergoing active consideration by the Strategic Advisory Group of Experts (SAGE) and that further updates will be available in the near future.
2. The TAG commends the Philippines on the licensing and introduction of dengue vaccine to selected cohorts of children in three regions of the Philippines as a school-based programme targeting students in Grade 4 who are at least 9 years of age.
3. The TAG notes that efficacy estimates of the currently available vaccine are serotype-specific, differ by underlying dengue serostatus (lower efficacy among those who are seronegative), and range from ~50% to ~85%, with an overall efficacy of ~65%. This is lower than most other vaccines used in the EPI and is expected under field conditions to reduce dengue disease by 20–30% in the long-term in moderate-to-high transmission settings. Further, efficacy is lower in children under 9 years of age, possibly because they are more likely to be seronegative for dengue than persons 9 years and older. The TAG also notes that there was an increase in hospitalization for dengue disease in the third year following vaccination among children aged 2–5 years. The TAG considers that the safety signal in young children may suggest there is an increased risk of severe dengue cases among persons 9 years and older, which could impact public confidence in the vaccine and the immunization programme as a whole.

2.2. Recommendations for Member States

2.2.1. Sustaining polio-free status and implementation of polio endgame strategies

1. The TAG recommends that all countries analyze and fill population immunity gaps by strengthening routine vaccination with polio vaccines and conducting polio supplementary immunization activities.
2. The TAG recommends that all countries improve surveillance for acute flaccid paralysis cases and conduct active surveillance especially in underperforming areas as outlined by the 21st Meeting of the Regional Commission for the Certification of Poliomyelitis Eradication in the Western Pacific. In addition, all countries and areas should notify in a comprehensive and timely manner all type 2 polioviruses detected from all sources, including environmental surveillance, as prompt detection/reporting of type 2 is critically important in the post-switch phase.
3. The TAG recommends that all countries ensure the completion of a national policy for the timely and comprehensive response to polio events/outbreaks in line with the Global Polio Eradication Initiative guiding documents.
4. The TAG recommends that all countries develop strategies to address gaps in population immunity against type 2 poliovirus due to delayed introduction or stock-out of IPV, including prioritization of IPV allocation to high-risk areas, and exploration of the programmatic feasibility of using IPV as a fractional dose via intradermal administration.
5. The TAG recommends that all countries authorize the importation and use of mOPV type 2 based on WHO prequalification and/or by providing an emergency waiver that permits

importation and use of the vaccine for emergency response, in order to respond within 14 days of a confirmed outbreak, and in accordance with the poliovirus type 2 outbreak response protocol.

6. The TAG recommends that all countries comply with the requirements of GAPIII Phase 1 (second part) and identify, appropriately handle and store materials that are infectious or potentially infectious with OPV type 2 and OPV type 2-like, Sabin type 2 and Sabin type 2-like viruses by the end of December 2016.

2.2.2. Hepatitis B accelerated control

1. The TAG urges all countries and areas to implement national policies for hepatitis B vaccination for health-care workers as part of a comprehensive health-care worker vaccination programme. Delaying the implementation of these policies in this high-risk group serves as a great risk to patient care and disease transmission.
2. The Global Health Sector Strategy on Viral Hepatitis 2016–2021 calls for a 90% reduction in incidence. Given that the Region has reached less than 1% regional prevalence among children 5 years of age, the TAG recommends that every country and area reach this 1% goal as soon as possible. Additionally, the hepatitis B ERP should consider the feasibility of reducing the regional goal to 0.5% prevalence, understanding that additional guidance including planning for and conducting serosurveys will be necessary for adopting this potential post-2017 goal.
3. The TAG encourages countries that have been identified as requiring programme improvement during the Workshop on Improving and Monitoring Hepatitis B Birth Dose Vaccination, namely Cambodia, Kiribati, the Lao People's Democratic Republic, Papua New Guinea, the Philippines, Solomon Islands, and Viet Nam, develop short- and long-term plans to programmatically improve birth dose and HepB3 coverage.
4. The TAG endorses the 2016 ERP vaccine-related recommendations, including: ministries of health should encourage the delivery of babies in health facilities, help strengthen the coordination between EPI and MCH for timely administration of hepatitis B birth dose and ensure effective monitoring and reporting of birth-dose coverage.

2.2.3. Japanese encephalitis (JE) accelerated control

1. The TAG recommends that JE incidence of less than 0.5 cases per 100 000 population in the targeted population (typically children under 15 years old) in affected areas (national and subnational) be the primary target for JE vaccination programmes to achieve accelerated control of JE in the Region. Incidence is a direct measure of disease occurrence and an incidence target will allow monitoring of JE vaccination programmes. Implementing an incidence target will require that Member States have high-quality JE surveillance so that incidence can be measured accurately.
2. The TAG recommends that for Member States that do not have high-quality JE surveillance, coverage of $\geq 95\%$ with primary JE vaccine series among the targeted population (typically children under 15 years old) in affected areas (national and subnational) be an intermediate target to achieve accelerated control of JE in the Region.
3. The TAG recommends that the primary strategy to achieve accelerated control of JE in the Region be introduction of JE vaccine into the routine immunization programme, using a phased approach depending on resources and capacities of countries.

2.2.4. Measles and rubella elimination

1. The TAG encourages Member States to continue to make efforts to increase coverage achieved with routine and supplemental administration of measles–rubella (MR) vaccine.
2. The TAG reaffirms its 2015 recommendation to establish a regional rubella elimination target date of 2020.
3. The TAG encourages countries to update or develop national strategies and plans of action for measles and rubella elimination. The draft Measles and Rubella Elimination in the Western Pacific - Regional Strategies and Plan of Action may serve as a valuable resource to Member States.
4. The TAG encourages countries to establish and maintain a platform to provide immunizations in the second year of life as an opportunity to reach all children, including those who are hard to reach, with MR and other scheduled vaccines and for catch-up immunizations for under-immunized children, as needed. To prevent measles virus transmission among preschool-aged children who are at highest risk of dying from measles, the second routine dose should be given in the second year of life.
5. The TAG encourages countries and areas to monitor and track coverage for the second dose of MR, to document the drop-out rate between the first and second doses of MR, and to work to reduce the drop-out rate. The WHO Regional Office for the Western Pacific should inventory which countries and areas have programme policy restrictions that limit vaccinations offered after 12 months of age and should work with countries and areas to remove these barriers to vaccination.
6. The TAG reiterates its 2014 recommendation that for countries experiencing measles outbreaks, supplementary vaccine doses should be considered for unvaccinated children aged 6 months and older who are not yet age eligible for the first dose of measles-containing vaccine (MCV1) in the national immunization programme and who are at high risk of exposure to the measles virus such as in outbreak settings or expected travel to measles-affected areas. Children who receive supplementary measles vaccine doses prior to the country's recommended age for MCV1 should continue to receive the two doses of MR according to the national immunization schedule. School entry should be used as an opportunity to ensure that all children have two documented doses of MR prior to school entry.
7. TAG encourages all countries to implement school-based programmes to check immunization records to maximize immunization coverage through catch-up immunization as needed. China and the Republic of Korea have successfully implemented the strategy. The recently published experience of China in the use of school-based checks of immunization records should be distributed to all countries by the Regional Office for the Western Pacific as an example of what can be achieved.
8. Appropriate infection control measures and health-care facility practices should be implemented to prevent transmission of measles and rubella in the health-care settings, especially in hospitals. These plans should include strategies to ensure that all health workers are immune to measles and rubella.

2.2.5. Maternal and neonatal tetanus elimination

1. The TAG recommends that the two remaining countries implement required actions to achieve the validation of MNTE as soon as possible:
 - a. The Philippines should implement the recommended tetanus toxoid supplemental immunization activities by the end 2016 in order to achieve national validation of MNTE; and
 - b. Papua New Guinea should move forward with the pre-validation assessment and validation survey as soon as possible.

2. All countries and areas should maintain elimination status by regularly reviewing the WHO/UNICEF district data of core and surrogate indicators for maternal and neonatal tetanus and by taking appropriate corrective actions in coordination with maternal, neonatal and child health programmes.
3. Every case of maternal and neonatal tetanus represents a sentinel event and should be thoroughly investigated including an assessment of the tetanus vaccination status among women of reproductive age residing in the same community to determine underlying risk factors and to assess possibility of implementing corrective actions.
4. All remaining countries that have not yet done so are encouraged to use vaccine combinations containing diphtheria toxoid and tetanus toxoid, rather than tetanus toxoid alone, when immunization against tetanus is indicated.
5. The TAG recommends that school-based immunization of tetanus–diphtheria vaccinations for both boys and girls should be considered as part of a national schedule to provide protection against tetanus and diphtheria.

2.2.6. Strengthening routine immunization systems-equity and sustainability

1. The TAG recommends that all Member States develop strategies to address gaps in vaccination and immunization services, particularly at subnational level, focusing on high-risk populations including underserved populations, the urban poor, minority ethnic groups, hard-to-reach and mobile populations. Further, the TAG encourages identifying and reducing missed opportunities for vaccination and a life-course approach to close the gaps in immunization services.
2. The TAG reiterates the recommendation of the 24th TAG:
 - a. Establishing an immunization visit platform in the second year of life to deliver scheduled vaccines such as DTP4 and MCV2, as well as providing catch-up vaccination for those vaccine doses missed during the first year of life; and
 - b. Establishing routine school immunization record checks and follow-up vaccinations with missed doses of measles, rubella and other vaccines so all children can enter school fully protected from vaccine-preventable diseases.
3. The TAG recommends Member States to work together with WHO and partners to ensure vaccine security and avoid stock-outs through regular vaccine forecasting, timely procurement and adequate resource allocation. It encourages countries to ensure best use of middle-income country strategies and V3P platform to overcome potential risks to vaccine security.

2.2.7. Strengthening evidence-based immunization decision-making

1. The TAG encourages Member States without NITAGs or equivalent immunization decision-making bodies to consider establishing such mechanisms.
2. The TAG recommends that Member States with NITAGs or equivalents consider evaluating their processes and effectiveness and identifying ways to strengthen them.
3. The TAG recommends that Member States, WHO and partners enhance linkages among NITAGs and consider creating a regional network in order to address common technical issues and develop NITAG capacity.

2.2.8. Strengthening routine immunization – Data quality

1. The TAG reiterates that Member States are urged to sustain and improve the timeliness, consistency and completeness of annual reporting of indicators listed in the WHO-UNICEF Joint Reporting Form, including financing indicators and vaccine price and procurement information through V3P platform.

2. The TAG recommends that Member States conduct data quality reviews, through regular desk reviews of national and subnational immunization coverage data, including assessment of denominators, and periodic health facility and district-level data quality assessment (DQS) as routine programme activity and/or through external support as stand-alone DQS or combined with EPI reviews.
3. The TAG recommends that Member States develop data improvement plans based on the findings of the desk reviews, including coverage surveys if appropriate.
4. The TAG encourages Member States to strengthen coordination with government stakeholders in charge of the health information system and target population registration in order to more accurately report vaccination coverage.
5. The TAG encourages Member States to explore the possibility of setting up an electronic immunization registry based on complete population database, through coordination with government stakeholders involved in the registration of target population, within and outside the health sector.

2.2.9. Strengthening vaccine safety surveillance and regulatory capacity

1. The TAG urges Member States to share best practices and lessons learnt in strengthening the vaccine/immunization safety surveillance systems including AEFI surveillance and NRA's adverse drug reactions surveillance through the NRA Alliance, considering the importance of immunization safety practices to maintain high-quality immunization services;
2. The TAG urges Member States to make continuous effort to strengthen AEFI surveillance through strengthening vaccine vigilance institutional mechanisms as appropriate, analysing the capacity gap by adopting root-cause analysis, self-assessment, developing and updating guidelines on vaccine safety surveillance, providing national and subnational trainings, establishing/institutionalizing national vaccine/immunization safety causality committees and enhancing analytical capacity.
3. The TAG urges Member States to continue timely and effective responses to vaccine/immunization safety incidents and to share the information through regional and global vaccine safety surveillance networks.
4. The TAG urges Member States to continue improving cold-chain capacity and logistics through periodic effective vaccine management assessment and update of national improvement plan.
5. The TAG urges Member States to strengthen vaccine regulatory systems, make continuous improvement and implement resolution WHA67.20 on regulatory system strengthening for vaccines as appropriate.
6. The TAG urges Member States to engage in and strengthen the regional alliance of national regulatory authorities, recognizing the importance of collaboration to pool regulatory capacities to promote greater access to quality, safe, efficacious and affordable vaccines.
7. The TAG urges Member States to support establishing effective vaccine and immunization safety communication systems in low- and middle-income countries in the Region.
8. The TAG urges Member States to address vaccine access issues by facilitating research and development, technology transfer, and legislating clinical trial oversight where the regulatory function is deficient.

2.2.10. Evidence-based introduction of new vaccines

1. The TAG advises each Member State to develop a national plan for evidence-based introduction of new vaccines. NITAGs or equivalent should play a central role in making recommendations to government about introduction of new vaccines. This plan could be part of the comprehensive multi-year plan for immunization or other health plans.
2. The TAG again urges Member States in which surveillance includes laboratory confirmation for diseases targeted by new vaccines to monitor and improve the quality of surveillance implementation.
3. Noting that in the context of the introduction of new vaccines, the perception that multiple injections during one visit is a problem, and noting the April 2015 SAGE recommendations on the issue of multiple injections, the TAG recommends that countries should neither modify recommended immunization schedules nor add additional visits for vaccine delivery solely for the purpose of preventing multiple injections during the same visit when such modifications are not evidence-based.

2.2.11. Dengue

1. The TAG recommends that, at present, countries and the Region should take a cautious approach to consideration of the use of dengue vaccine. The TAG recommends that any consideration should closely follow the advice in the current position paper, new information on safety and efficacy of these vaccines, and additional evaluations and policy recommendations of the SAGE.
2. The TAG recommends that the Philippines provide regular updates on the effectiveness, safety and implementation of the dengue vaccine using a school-based platform.

2.3. Recommendations for WHO Secretariat

2.3.1. Sustaining polio-free status and implementation of polio endgame strategies

1. The TAG recommends WHO to urge additional manufacturers to prequalify IPV as soon as possible to decrease the risk of global shortages and maintain long-term vaccine security.

2.3.2. Hepatitis B accelerated control

1. The TAG encourages the WHO Regional Office of the Western Pacific to widely publicize the success of hepatitis B vaccination programmes across the Region in averting 7 million deaths and 37 million chronic infections that would have otherwise occurred between 1990 and 2014. Having accomplished this among many Member States ahead of the 2017 target is highly commendable and should be shared as part of this impressive vaccine success story.
2. The TAG reiterates its support for the use of hepatitis B vaccine outside the cold chain (OCC) for health facilities without functional cold chain, assuring proper monitoring conditions are in place.
3. The TAG reiterates that manufacturers should be encouraged to relabel vaccine to allow its use in a controlled temperature chain (CTC). Relabelling vaccine for CTC use would particularly assist countries with weak NRAs in safely storing and transporting hepatitis B vaccine outside of the traditional 2-8 °C.
4. The TAG endorses the ERP's role in monitoring the ongoing performance of verified countries and their 2016 vaccine-related recommendation: that WHO to urge

procurement agencies to require vaccine manufacturers to include on their labels the suitability for CTC use of monovalent hepatitis B vaccines.

2.3.3. Japanese encephalitis (JE) accelerated control

1. The TAG recommends the WHO Regional Office for the Western Pacific to consult with experts on JE control and prevention and also with staff from the WHO Regional Office for South-East Asia involved in JE control and prevention to set a timeline for achieving the regional accelerated control target.
2. The TAG reiterates the recommendations of the 22nd, 23rd and 24th TAGs that JE surveillance with laboratory confirmation should be further strengthened in endemic areas of the Western Pacific Region, and sentinel surveillance should be systematized to facilitate reporting at the regional level. Additional resource mobilization will be needed to implement this recommendation.
3. The TAG recommends the WHO Regional Office for the Western Pacific to conduct an assessment of resources needed to expand use of the JE surveillance structured tool for the assessment of implementation in countries that have not yet achieved a high degree of JE control.

2.3.4. Measles and rubella elimination

1. By the end 2016, WHO should finalize the draft Measles and Rubella Elimination in the Western Pacific - Regional Strategies and Plan of Action through further consultation with TAG, national immunization programmes of Member States and partners.
2. WHO should submit the final Measles and Rubella Elimination in the Western Pacific - Regional Strategies and Plan of Action to the 68th session of WHO Regional Committee for the Western Pacific in 2017 for review and endorsement.
3. TAG requests WHO to consult with Member States for setting the target year for regional rubella elimination.
4. WHO should complete revisions of the Guidelines on Verification of Measles Elimination in the Western Pacific Region (2013) through further consultation with the Regional Verification Commission for Measles Elimination in the Western Pacific (RVC), Subregional Committee for the Verification of Measles Elimination in the Pacific island countries and areas (SRVC) and national verification committees (NVCs) to include monitoring progress of rubella elimination along with measles elimination in each country and area.

2.3.5. Strengthening routine immunization systems – equity and sustainability

1. The TAG recommends the development of a comprehensive global and regional guideline to support countries to overcome vaccine hesitancy. It encourages Member States to proactively work on identifying and addressing country-specific vaccine hesitancy issues.
2. The TAG reiterates its support to ensure sustainability of achievements and continuing efforts to achieve the goals of the GVAP and the Regional Framework for GVAP Implementation in the Western Pacific. TAG endorses the usefulness of Global Routine Immunization Strategies and Practices (GRISP) in strengthening country routine immunization programmes towards achieving GVAP targets.

2.3.6. Strengthening evidence-based immunization decision making

1. The TAG recommends that WHO and partners give particular attention and support to Pacific island countries and develop innovative means through which to improve their immunization policy-making, such as assessing feasibility of a subregional TAG or developing other suitable mechanisms.

2.3.7. Strengthening vaccine safety surveillance and regulatory capacity

1. The TAG recommends exploration of the optimization of regional expertise resources to support the performance of vaccine/immunization safety surveillance systems of middle-income countries in the Region.
2. The TAG recommends exploration of means to support Pacific island countries and areas for AEFI causality assessment committees to include outreach and training of medical personnel to appropriately and accurately report adverse events associated with the administration of a vaccine.
3. The TAG recommends continuation of vaccine pharmacovigilance system assessments using a common vaccine–medicine assessment tool and to support capacity-building for low- and middle-income countries.
4. The TAG supports continued improvement of effective vaccine management in public health medicines supply system and vaccine regulatory systems through implementation of EVM improvement plan and NRA institutional development plan.

2.3.8. Evidence-based introduction of new vaccines

1. The TAG requests WHO to provide technical support and capacity-building for the development of national plans for evidence-based introduction of new vaccines and to assess and improve the quality of surveillance implementation.

Update on the Gavi Alliance Board meeting 22-23 June 2016

Among the key decisions of the Gavi Board were:

The Gavi Alliance Board, using available resources from the current strategic period, and contingent upon WHO securing funding from other sources to fully finance the Malaria Vaccine Pilots: Approval in principle an amount of up to US\$ 27.5 million (equivalent to half of the funding request) for Phase 1 of the **WHO-led Malaria Vaccine pilots** to be implemented during 2017-2020.

The Board noted that this investment is contingent upon:

- i. Other funders contributing an equivalent amount to cover the pilot costs;
- ii. Independent review of the proposed budget amount ensuring that this is being done as cost effectively as possible;
- iii. Further assessment of the selection of pilot settings;
- iv. Close engagement with the Global Fund and UNITAID including through the proposed Funders Forum;
- v. WHO seeking input from Alliance partners in the planning and implementation of the pilots;
- vi. Communication that this investment is for implementation evaluation of a newly licensed vaccine as distinct from R&D;
- vii. Clear communication that this recommendation does not constitute a precedent for future funding related to the implementation of the malaria vaccine regardless of the outcome of the pilots, nor for future funding of similar pilots for other vaccines;
- viii. Quarterly reports, including active monitoring of key risks, to the PPC, and a detailed report to the PPC and Board on progress no later than 2019.

Agreement to a portion of the already approved **Gavi contribution to the global oral cholera vaccine stockpile** being used for operational costs for Gavi-supported, for which the estimated costs are US\$ 20 million in the period 2016-2018.

Approval of an amount of up to US\$ 15 million of **bridge funding to meet meningitis emergency outbreak** needs of the 26 countries in the African meningitis belt in the 2016-2017 and 2017-2018 transmission seasons to be managed through the Meningitis International Coordination Group (ICG). The bridge funding amount includes estimated costs for the procurement of polysaccharide and conjugate vaccines, devices and shipment and operational cost.

Agreed that Gavi and countries shall co-finance Japanese Encephalitis vaccine used in routine vaccination programmes.

Approval of the Framework guiding implementation of **Gavi's Health System and Immunisation Strengthening support**.

Gavi's strategic partnership with India

Historically, given its size, Gavi has limited its support to catalytic funding to India. Recognising the country's strong political commitment for universal immunisation coverage and the country's forthcoming transition out of Gavi support, the Board approved a comprehensive Gavi-India partnership strategy. This partnership is designed to help India achieve greater and more equitable coverage, strengthen vaccine delivery systems in poorly performing regions, and accelerate rollout of new vaccines, while also ensuring that a robust plan is in place for India's transition including scaling up domestic investment in immunisation. The strategy calls for stronger collaboration with vaccine manufacturers in India who are also a key source of supply for Gavi, accounting for nearly 60% of our vaccine volume. This strengthened collaboration between Gavi and India will help manage global supply security of vaccines and optimise cost-savings for all Gavi countries.

Partners' Engagement framework (PEF)

In June, the Board approved the structure and governance process for the Partners' Engagement framework (PEF) – a new mechanism for the Alliance to design, coordinate, and fund partners' technical support. The Board approved the funding envelopes to make the PEF operational in 2016 which will focus primarily on addressing countries' needs and enhancing accountability for outcomes at country level.

Data strategic focus area

As part of the 2016-2020 strategy, the Alliance identified six strategic focus areas (SFAs) where cross-cutting strategies might deliver transformational impact: supply chain; data quality, availability and use; in-country leadership, management and coordination; demand promotion; in-country political will; as well as financial and programmatic sustainability. The Board discussions focused on the data SFA, as the supply chain SFA was previously approved and other SFAs will follow in 2016 if a transformational theory of change is developed.

The data SFA, developed by the Secretariat in collaboration with the Alliance partners, defines three areas of focus to guide Gavi engagement in data: immunisation delivery, coverage and equity, vaccine-preventable diseases (VDP) surveillance, and vaccine safety surveillance and response. The Board approved this approach, which aims to be country-centric and respond to data needs at country level.

Gavi's 2016-2020 Strategy goal level indicators and targets

The Board approved the remaining strategic goal-level indicators not included among the set already approved by the Board in June 2015.



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Contents

- 341 Global Advisory Committee
on Vaccine Safety, 15–16 June
2016

Sommaire

- 341 Comité consultatif mondial
de la sécurité des vaccins,
15–16 juin 2016

Global Advisory Committee on Vaccine Safety, 15–16 June 2016

The Global Advisory Committee on Vaccine Safety (GACVS), an independent expert clinical and scientific advisory body, provides WHO with scientifically rigorous advice on vaccine safety issues of potential global importance.¹ GACVS held its 34th meeting in Geneva, Switzerland, on 15–16 June 2016.² The Committee examined 3 generic issues: (i) a new initiative to promote health product vigilance in low- and middle-income countries (LMICs); (ii) the harmonization of the definition of health events for pharmacovigilance studies in pregnancy and early childhood; and (iii) a proof-of-concept study to assess rare events through multi-country collaboration. The Committee also reviewed vaccine-specific safety issues on routine infant vaccination in India and initial post-licensure data related to dengue vaccine.

New initiative on health product vigilance

Access to novel medical products in LMICs is increasing. New treatments are available, or in preparation, for HIV/AIDS, tuberculosis and malaria. Likewise, vaccines targeting cervical cancer, diarrhoeal diseases and conditions that prevail mostly in LMIC, such as Ebola virus disease, dengue, epidemic meningitis and malaria, are at various stages of implementation in those countries.

Comité consultatif mondial de la sécurité des vaccins, 15–16 juin 2016

Le Comité consultatif mondial de la sécurité des vaccins (GACVS) est un organe consultatif indépendant composé d'experts cliniques et scientifiques qui fournissent à l'OMS des conseils d'une grande rigueur scientifique sur des problèmes de sécurité des vaccins susceptibles d'avoir une portée mondiale.¹ Le GACVS a tenu sa 34^e réunion à Genève (Suisse) les 15 et 16 juin 2016.² Il a examiné 3 questions génériques: i) une nouvelle initiative pour promouvoir la vigilance à l'égard des produits sanitaires dans les pays à revenu faible ou intermédiaire; ii) l'harmonisation de la définition des manifestations indésirables dans les études de pharmacovigilance durant la grossesse et la petite enfance; et iii) une étude de preuve de concept pour évaluer les manifestations rares au travers d'une collaboration multi-pays. Le GACVS a également examiné une étude de l'innocuité des vaccins dans le cadre de la vaccination systématique des nourrissons en Inde, ainsi que les premières données post-homologation du vaccin contre la dengue.

Nouvelle initiative de vigilance à l'égard des produits sanitaires

L'accès aux produits médicaux novateurs progresse dans les pays à revenu faible ou intermédiaire. De nouveaux traitements contre le VIH/sida, la tuberculose et le paludisme sont désormais disponibles ou sont en passe de l'être. De même, des vaccins contre le cancer du col de l'utérus, les maladies diarrhéiques et certaines affections touchant principalement les pays à revenu faible ou intermédiaire, comme la maladie à virus Ebola, la dengue, la méningite épidémique et le paludisme, ont atteint divers stades de déploiement dans ces pays.

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¹ See No. 41, 1999, pp. 337–338.

² GACVS invited additional experts to present and discuss evidence related to particular topics. These experts included persons affiliated with: Bill & Melinda Gates Foundation, Seattle WA, USA; GAVI Alliance, Geneva, Switzerland; INCLEN Trust International, New Delhi, India; Erasmus University, Rotterdam, The Netherlands; P-95 Heverlee, Belgium; St George's University, London, United Kingdom; Department of Health, Manila, The Philippines; Cincinnati Children's Hospital Medical Center, Cincinnati OH, USA; and Sanofi Pasteur, Lyon, France.

¹ Voir N° 41, 1999, p. 337-338.

² Le GACVS a invité d'autres experts à présenter et à analyser les données relatives à des sujets particuliers. Il s'agissait de personnes affiliées aux organismes suivants: Fondation Bill et Melinda Gates, Seattle WA, États-Unis d'Amérique; Alliance GAVI, Genève, Suisse; INCLEN Trust International, New Delhi, Inde; Université Erasmus, Rotterdam, Pays-Bas; P-95 Heverlee, Belgique; St George's University, Londres, Royaume-Uni; Ministère de la santé, Manille, Philippines; Cincinnati Children's Hospital Medical Center, Cincinnati OH, États-Unis d'Amérique; et Sanofi Pasteur, Lyon, France.

The availability of post-licensure data is essential for local regulators as well as for public health programmes in developing strategies based on adequate benefit and risk analyses. For products that are used globally, safety data are usually available from high-income settings only, and differ from LMICs in terms of their health-care systems, health profiles and population demographics. While many LMICs participate as national centres in the WHO Programme for International Drug Monitoring (PIDM), their capacity to undertake data collection and contribute to the international database of drug safety may be limited. For example, with vaccines, 60% of the PIDM database comprises reports from some countries in Europe, and the USA, and this may not fully satisfy the needs of local authorities with limited capacity to analyse data and take necessary action.

The Bill & Melinda Gates Foundation (BMGF) has acknowledged the need to build pharmacovigilance capacity in LMICs. In 2013, the BMGF Safety Surveillance Working Group convened and highlighted the need to develop a strategy for post-marketing surveillance given the existing challenges.³ Their report called for leveraging existing scalable platforms (WHO PIDM and its network of national centres), using current standards for safety, and building on current harmonization platforms. The report also recommended devising a single system for both vaccines and medicines, with adjustments only when required.

The BMGF proposed support for the WHO Safety and Vigilance (SAV) team in implementing a strategy for LMICs that would include a regulators network to strengthen pharmacovigilance systems. This would involve continued work with other participants such as the GAVI Alliance (GAVI), UNICEF, PATH and sub-Saharan African regulatory agencies, as well as the engagement of industry to promote alignment between participants/agencies to support implementation as accountable license holders.

GAVI, meanwhile, has prioritized the monitoring of vaccine safety in its data strategy for 2020. The aims are to improve the ability to identify and investigate, to respond efficiently and effectively, and to address related public concerns. GAVI already funds a number of initiatives, partly through its grants for strengthening health systems for capacity-building in LMICs for the surveillance, investigation and management of adverse events following immunization (AEFI) and for the establishment of surveillance systems and the development of tools, guidelines and AEFI training. Surveillance which covers the safety of other drug products, including

La disponibilité de données post-homologation est essentielle pour les organismes de réglementation locaux, mais permet également aux programmes de santé publique d'élaborer des stratégies fondées sur des analyses fiables des risques et des avantages. Pour les produits utilisés à l'échelle mondiale, ces données sur l'innocuité ne proviennent souvent que des pays à revenu élevé, qui diffèrent des pays à revenu faible ou intermédiaire de par leur système de santé et leur profil sanitaire et démographique. De nombreux pays à revenu faible ou intermédiaire participent au programme OMS de pharmacovigilance internationale en tant que centres nationaux, mais leur capacité à assurer la pharmacovigilance et à contribuer à la base de données internationale peut s'avérer limitée. Par exemple, pour les vaccins, la base de données du programme de pharmacovigilance internationale est constituée à 60% de rapports provenant de quelques pays européens et des États-Unis d'Amérique, ce qui ne répond pas nécessairement pleinement aux besoins des autorités locales, dont la capacité à analyser les données et à réagir peut être limitée.

La Fondation Bill et Melinda Gates a reconnu le besoin de renforcer la capacité de pharmacovigilance dans les pays à revenu faible ou intermédiaire. Son groupe de travail sur la surveillance de l'innocuité, réuni en 2013, a émis un rapport soulignant la nécessité d'élaborer une stratégie de surveillance après la mise sur le marché, compte tenu des difficultés existantes.³ Ce rapport appelle à tirer parti des plateformes modulaires existantes (programme OMS de pharmacovigilance internationale et son réseau de centres nationaux) en appliquant les normes actuelles de sécurité et en s'appuyant sur les plateformes actuelles d'harmonisation. Il préconise également d'envisager la mise en place d'un système unique applicable aussi bien aux vaccins qu'aux médicaments, à adapter au cas par cas uniquement si nécessaire.

La Fondation Bill et Melinda Gates a proposé d'appuyer les activités menées par l'équipe Sécurité et vigilance de l'OMS pour mettre en œuvre une stratégie de pharmacovigilance reposant sur un réseau d'organismes de réglementation dans les pays à revenu faible ou intermédiaire afin de renforcer les systèmes de pharmacovigilance. Cela impliquera de poursuivre les efforts de collaboration avec d'autres participants tels que l'Alliance GAVI, l'UNICEF, le Programme de technologie appropriée pour la santé (PATH) et les organismes de réglementation d'Afrique subsaharienne et de favoriser l'engagement des membres de l'industrie à promouvoir la conformité pour appuyer la mise en œuvre, assumant leur responsabilité en tant que bénéficiaires de l'homologation.

L'Alliance GAVI a récemment accordé la priorité à la surveillance de la sécurité des vaccins dans sa stratégie sur les données pour 2020, laquelle vise à renforcer les capacités à identifier les préoccupations du public en matière de sécurité des vaccins, à mener des enquêtes et à intervenir de manière efficace. Au travers de subventions de renforcement des systèmes de santé, l'Alliance GAVI finance déjà en partie de nombreuses initiatives de renforcement des capacités dans les pays à revenu faible ou intermédiaire pour améliorer la surveillance, l'étude et la gestion des manifestations postvaccinales indésirables (MAPI), établir des systèmes de surveillance et élaborer des outils, des lignes directrices et des programmes de formation sur les

³ Bill & Melinda Gates Foundation. A report of the safety surveillance working group. Available at: https://docs.gatesfoundation.org/documents/SSWG%20Final%20Report%2011%2019%2013_designed.pdf, accessed June 2016.

³ Bill & Melinda Gates Foundation. A report of the safety surveillance working group. Disponible sur https://docs.gatesfoundation.org/documents/SSWG%20Final%20Report%2011%2019%2013_designed.pdf, consulté en juin 2016.

substandard and falsified drugs and vaccines, remains a specific challenge.

The BMGF, SAV and GAVI presented strategies and approaches relating to vaccine safety to GACVS. Additionally, GAVI set out its resourcing plans including funding for its Data Strategic Focus Area (SFA) and vaccine safety activities. Currently, GAVI Data SFA does not include enhanced investigation capacity and guidance on communication and response; this is an area that needs to be addressed.

GACVS acknowledged both the increased attention being given to the pharmacovigilance of drug products – especially to capacity-building in safety monitoring, and to the work of WHO SAV and its promotion of, and collaboration on, vigilance activities with public health programmes, and the response to safety concerns and international crises. The aims of the BMGF in its support for pharmacovigilance and vaccine safety were also recognized, and included capacity-building through country training supported by GAVI and WHO SAV – training that has recently focused on countries in sub-Saharan Africa. GACVS also identified the very different pharmacovigilance needs of vaccine products compared with other drug products, especially in LMICs where programme delivery of vaccines and drugs may vary and pose unique challenges. Merging is to be considered with caution, although lessons learned from vaccine vigilance could be applied to some of the unique drug product classes as outlined above.

GACVS welcomes future collaboration with, and contribution to, this endeavour as well as providing input to identified gaps and evolving priorities.

Serious AEFI during primary infant vaccination series in South India

India is currently using pentavalent (DwPT-HepB-Hib) vaccine from local manufacturers. The vaccination series is carried out nationwide via a stepwise introduction process initiated in December 2011. To accompany this effort and address safety concerns on the potential of AEFI, the Indian authorities, with INCLEN Trust International, conducted a prospective dynamic cohort study in 2 southern districts (Kollam, Kerala and Coimbatore, Tamil Nadu). This study evaluated the association between routine pentavalent and oral poliovirus (OPV) vaccination and all-cause deaths and hospitalizations (referred to as serious AEFI) among infants after receipt of each of the 3 doses of vaccine in the primary immunization schedule. The 2 districts were selected on the basis of their low infant mortality (reducing the background of coincidental events), high coverage with the primary vaccination series, well established use of

MAPI. La surveillance de l'innocuité d'autres produits pharmaceutiques demeure particulièrement difficile, notamment face aux problèmes associés à l'utilisation de médicaments de qualité inférieure ou falsifiés, problèmes qui concernent aussi les vaccins.

Le GACVS a pris connaissance des stratégies et des approches adoptées par la Fondation Bill et Melinda Gates, l'équipe Sécurité et vigilance de l'OMS et l'Alliance GAVI dans ce domaine. En outre, l'Alliance GAVI a présenté son plan d'allocation de ressources pour la sécurité des vaccins, qui comprend un financement du domaine stratégique prioritaire relatif aux données et un financement associé pour les activités de sécurité des vaccins.

Le GACVS a noté l'attention accrue portée à la pharmacovigilance des produits pharmaceutiques, et en particulier au renforcement des capacités en matière de surveillance de l'innocuité. Il a salué le travail accompli par l'équipe Sécurité et vigilance de l'OMS pour promouvoir les activités de vigilance en collaboration avec les programmes de santé publique et remédier aux problèmes liés à la sécurité des produits, y compris dans les situations de crise de portée internationale. Le GACVS a souligné que les objectifs proposés par la Fondation Bill et Melinda Gates en matière de pharmacovigilance confortent les efforts engagés depuis de nombreuses années dans le domaine de la sécurité des vaccins, notamment le renforcement des capacités au moyen d'une formation offerte dans les pays avec l'appui de l'Alliance GAVI et de l'équipe Sécurité et vigilance de l'OMS, formation qui s'est récemment concentrée sur les pays d'Afrique subsaharienne. Le GACVS a également fait valoir que les besoins de pharmacovigilance sont très différents pour les produits vaccinaux par rapport aux autres produits pharmaceutiques, en particulier dans les pays à revenu faible ou intermédiaire où l'administration programmatique des vaccins et des médicaments peut varier et poser des difficultés particulières. Une fusion ne devrait être envisagée qu'avec prudence, bien que les enseignements tirés de la vigilance pour les vaccins puissent être appliqués à certaines catégories uniques de médicaments évoquées ci-dessus.

Le GACVS se réjouit de contribuer pleinement à ces efforts et d'apporter un éclairage sur les lacunes identifiées et l'évolution des priorités.

MAPI graves durant la série de primovaccination du nourrisson en Inde du Sud

L'Inde utilise actuellement, un vaccin pentavalent (DTCe-HepB-Hib) fabriqué localement. La série de doses de primovaccination est administrée à l'échelle nationale dans le cadre d'un processus d'introduction par étapes engagé en décembre 2011. Pour appuyer cet effort et répondre aux préoccupations concernant le risque de MAPI, les autorités indiennes, en collaboration avec INCLEN Trust International, ont mené une étude de cohorte dynamique et prospective dans 2 districts du sud du pays – Kollam (Kerala) et Coimbatore (Tamil Nadu). Ce projet visait à évaluer le lien entre la vaccination systématique – par le vaccin antipoliomyélitique oral (VPO) et le vaccin pentavalent – et les décès et hospitalisations toutes causes confondues (désignés comme «MAPI graves») chez les nourrissons après l'administration de chacune des trois doses prévues au calendrier de primovaccination. Ces deux districts ont été choisis en raison de leur faible mortalité infantile (pour réduire le bruit de fond dû aux manifestations de coïncidence), de leur forte couverture par la série de primovac-

pentavalent vaccine, and robust primary health-care infrastructure.

The primary study objective compared all-cause death and hospitalization rates at 0–7 days versus 22–28 days after each vaccine dose administered. Secondary objectives included comparing all-cause death and hospitalization between 8–14 days and 15–21 days versus 22–28 days after vaccination. For infants with a delayed second or third dose of vaccine, the risk of serious AEFI was estimated for the period to the following dose, or at 24 weeks of age, or death, whichever occurred first. Infants were enrolled at the time of their first dose of pentavalent and OPV vaccines and followed weekly until 4 weeks after their third dose of pentavalent vaccine. In addition to collecting information on illnesses, data were collected for subsequent hospitalizations and deaths through weekly contact with the infant's family. The information was entered electronically at interview. An International Advisory Group provided technical input on the protocol and statistical plan, reviewed study progress during several field visits, and reviewed preliminary study findings. In addition to analysing the project as a cohort study, secondary analyses will also include a self-controlled case series. Implementation of the study occurred between September 2014 and May 2016. In total over 30 000 infants were enrolled and followed weekly until 4 weeks after the third dose of vaccine. Data collection is complete and data analysis is ongoing, with plans for publication.

GACVS acknowledged the quality of the study implementation, the completeness of the follow-up and the thorough and timely data collection system. The primary analysis showed no safety concerns. This study will help to better characterize factors associated with untoward events temporally related with vaccination early in life and will provide a robust empirical basis to illustrate the coincidental occurrence of serious AEFI and quantify the frequency with which those events can be expected.

Global Alignment of Immunization safety Assessment in pregnancy (GAIA) project

Vaccination during pregnancy offers mothers and their infants effective protection against infectious diseases. However, due to the heterogeneity in the definitions of terms used to assess vaccine safety, data collection methods and their presentation, comparing results across studies and settings presents challenges. Thus, the harmonization of terms, disease concepts and the use of standardized case definitions of key events related to safety monitoring of vaccines will facilitate comparability of outcomes across studies.

In 2014, WHO convened an expert consultation to a) review existing obstetrical and paediatric adverse event case definitions and guidance documents; b) prioritize terms for key events for continuous monitoring of vaccine safety in pregnancy; c) develop concept

cination, de leur utilisation bien établie du vaccin pentavalent et de leur infrastructure solide pour les soins de santé primaires.

L'objectif principal de l'étude consistait à comparer les taux de décès et d'hospitalisation toutes causes confondues à 0-7 jours après l'administration de chaque dose de vaccin par rapport à ceux observés à 22-28 jours. Les objectifs secondaires consistaient entre autres à comparer les taux de décès et d'hospitalisation toutes causes confondues observés à 8-14 jours et 15-21 jours par rapport à 22-28 jours. En cas d'administration retardée de la deuxième ou de la troisième dose de vaccin, le risque de MAPI grave est également estimé pour toute la période jusqu'à la prochaine dose, l'âge de 24 semaines ou le décès, selon la première de ces éventualités. Les nourrissons ont été inclus dans l'étude au moment de leur première dose de vaccin pentavalent et de VPO, puis ont fait l'objet d'un suivi hebdomadaire jusqu'à 4 semaines après l'administration de la troisième dose de vaccin pentavalent. Outre les informations sur les maladies contractées, les données sur les hospitalisations ou décès ultérieurs ont été recueillies grâce à des contacts hebdomadaires avec la famille du nourrisson. Ces informations ont été saisies sous forme électronique, dans des tablettes, lors des entretiens. Un groupe consultatif international était chargé de fournir un avis technique sur le protocole et le plan statistique, d'évaluer les progrès de l'étude à l'occasion de plusieurs visites sur le terrain et d'examiner les résultats préliminaires. Ce projet sera analysé non seulement en tant qu'étude de cohorte, mais donnera également lieu à des analyses secondaires des séries de cas autocontrôlées. L'étude a été mise en œuvre de septembre 2014 à mai 2016. En tout, plus de 30 000 nourrissons ont été inclus dans l'étude et ont fait l'objet d'un suivi hebdomadaire jusqu'à 4 semaines après l'administration de la troisième dose de vaccin. La collecte de données est achevée et l'analyse des données est en cours, en vue d'une publication.

Le GACVS a reconnu la qualité de la conduite de l'étude, l'exhaustivité du suivi et la rigueur et la rapidité de la collecte des données. L'analyse primaire n'a révélé aucun problème de sécurité. Cette étude permettra de mieux caractériser les facteurs associés à l'apparition de manifestations défavorables temporairement liées à la vaccination en début de vie. Elle fournira une base empirique solide pour illustrer l'apparition par coïncidence des MAPI graves et estimer la fréquence avec laquelle elles sont susceptibles de survenir.

Projet d'alignement mondial de l'évaluation de la sécurité des vaccins durant la grossesse (GAIA)

La vaccination durant la grossesse est un moyen efficace de protéger les mères et leurs nourrissons contre les maladies infectieuses. Cependant, du fait de l'hétérogénéité des définitions appliquées aux termes employés pour évaluer la sécurité des vaccins, ainsi que des méthodes de collecte et de présentation des données, il est difficile de comparer les résultats provenant d'études et de contextes différents. Pour faciliter la comparaison des résultats d'une étude à l'autre, il importe donc d'harmoniser les termes, les concepts et les définitions de cas normalisées utilisés pour caractériser les principales manifestations visées par la surveillance de la sécurité des vaccins.

En 2014, l'OMS a organisé une consultation d'experts pour a) examiner les définitions de cas actuellement appliquées aux manifestations obstétricales et pédiatriques indésirables, ainsi que les documents d'orientation en la matière; b) définir les termes prioritaires relatifs aux principales manifestations

definitions for these events; and d) recommend a core data set of key terms of events to be collected when monitoring safety of vaccines used in pregnancy. The consultation also recommended developing a guidance document for data collection, analysis and presentation of safety data, tools for harmonized data collection, data sharing, and the use of health-care data sets to strengthen safety surveillance.

The Global Alignment of Immunization safety Assessment in pregnancy (GAIA) network was formed to help establish a global, common understanding of outcomes and approaches to monitoring safety of vaccines used in pregnancy with particular focus on LMICs. GAIA has prepared draft guidelines – “Guidelines for collection, analysis and presentation of safety data in clinical trials of vaccines in pregnant women” on prioritizing data to be collected in studies of the use of vaccines in pregnancy, and to assist their applicability in various geographical, cultural and resource settings, including LMICs. The intention is also to optimize the use of data obtained from participants in clinical trials by improving data accuracy and comparability.

The guidelines are intended for all entities involved in the planning, evaluation, and implementation of studies on vaccines used in pregnancy. However, they are not regulatory in nature, and are not intended to replace established or mandated processes of adverse event reporting. In their current form, applying all recommended standards may thus prove complex for some settings.

The guideline document emphasizes 5 aspects of data collection for pregnancy vaccine trials: (i) collection of background data; (ii) pre-vaccination screening data; (iii) vaccine- and immunization-related data; (iv) follow-up monitoring data (including birth-related and neonatal data); and (v) adverse event monitoring data (including maternal, fetal and infant). While it may not be practical to pre-define and solicit all possible clinical and laboratory outcomes, a core dataset should be collected in all vaccine trials in pregnancy, where feasible. Two levels of priority for data collection have been defined: priority 1 – data considered important for the understanding of the trial results and/or required by national and/or international regulatory authorities; and priority 2 – data considered less important but helpful.

The guidelines prepared by GAIA were reviewed and discussed by the pregnancy subgroup of GACVS and at

devant faire l'objet d'une surveillance continue de la sécurité des vaccins pendant la grossesse; c) élaborer des définitions conceptuelles de ces manifestations; et d) recommander un ensemble de données de base des termes clés applicables aux manifestations indésirables à recueillir lors des activités de surveillance de la sécurité des vaccins administrés durant la grossesse. Durant la consultation, il a également été recommandé d'élaborer un document d'orientation sur la collecte, l'analyse et la présentation des données de sécurité, les outils permettant d'harmoniser la collecte des données, l'échange des données et l'utilisation d'ensembles de données sur les soins de santé pour renforcer la surveillance de la sécurité des vaccins.

Le réseau d'alignement mondial de l'évaluation de la sécurité des vaccins durant la grossesse (GAIA) a été établi pour favoriser une compréhension commune à l'échelle mondiale des résultats et des méthodes de surveillance de la sécurité des vaccins utilisés durant la grossesse, en mettant particulièrement l'accent sur les pays à revenu faible ou intermédiaire. Dans le cadre de cette initiative, un projet de lignes directrices, intitulé «Lignes directrices pour la collecte, l'analyse et la présentation des données de sécurité dans les essais cliniques sur les vaccins administrés aux femmes enceintes», a été élaboré pour fournir des orientations sur les données à recueillir en priorité dans les études portant sur les vaccins administrés durant la grossesse et pour donner des conseils sur leur applicabilité à divers contextes géographiques et culturels et divers niveaux de ressources, y compris dans les pays à revenu faible ou intermédiaire. L'objectif est également d'optimiser l'utilisation des données obtenues auprès des participants aux essais cliniques en améliorant l'exactitude et la comparabilité des données.

Ces lignes directrices sont destinées à toutes les entités participant à la planification, à l'évaluation et à la conduite d'études sur les vaccins administrés pendant la grossesse. Cependant, elles n'ont pas de caractère réglementaire et ne sont pas destinées à remplacer les processus établis et obligatoires de notification des manifestations indésirables. Sous leur forme actuelle, les normes recommandées pourront s'avérer difficiles à appliquer dans certains contextes.

Le document d'orientation met l'accent sur 5 aspects de la collecte de données dans les essais cliniques des vaccins administrés pendant la grossesse: i) collecte des données de base; b) données de dépistage avant la vaccination; c) données relatives au vaccin et à la vaccination, d) données de suivi (notamment données liées à la naissance et au nouveau-né); et e) données de surveillance des manifestations indésirables (chez la mère, le fœtus et le nourrisson). Bien qu'il ne soit pas toujours aisé de prédéfinir et de solliciter tous les résultats cliniques et biologiques possibles, il convient, dans la mesure du possible, de recueillir un ensemble de données de base dans tous les essais portant sur les vaccins durant la grossesse. Deux niveaux de priorité ont été définis pour la collecte des données – priorité 1: données jugées importantes pour la compréhension des résultats de l'essai et/ou requises par les autorités de réglementation nationales et/ou internationales; et priorité 2: données jugées moins importantes mais utiles.

Les lignes directrices préparées par GAIA ont fait l'objet d'un examen et d'une discussion par le sous-groupe du GACVS

the IABS⁴ “Harmonized Safety Monitoring of Immunization in Pregnancy International Consensus Conference” in March 2016, following which they were revised. GACVS reviewed the revised version and agreed that a global concerted approach was needed towards harmonized safety data collection in vaccine trials in pregnancy.

The Committee considered the GAIA guidelines timely and useful and noted that they should provide for flexibility regarding core data collection requirements as data collection in certain settings may not be feasible. Challenges related to infrastructure, availability of background data, changes in background rates or clinical standards in various settings should also be acknowledged, including the fact that the presence of researchers will affect some pregnancy-related outcomes. GACVS also noted the possibility of updating these guidelines which may also be applicable for safety monitoring in the context of observational studies. Furthermore, to test and facilitate their implementation, the Committee stressed the need for field testing and review, the generation of practical tools for investigators, capacity-building/training and a dissemination strategy.

Dengue vaccine update

GACVS last reviewed dengue vaccines in June 2015⁵ and considered the Phase III clinical trial and long-term safety data of the tetravalent dengue vaccine CYD-TDV (Dengvaxia, manufactured by Sanofi Pasteur). Short-term safety surveillance of common adverse events demonstrated that the vaccine is well-tolerated. However, GACVS noted particular safety concerns related to the observed risk of hospitalized and severe dengue among children aged 2–5 years during the third year following vaccination. GACVS also recommended monitoring the risk of severe dengue among individuals of all ages who are seronegative prior to immunization, as well as among immunocompromised and older individuals (>45 years of age).

In April 2016, SAGE published recommendations indicating who would benefit most from CYD-TDV vaccination and issued guidelines for post-licensure surveillance.⁶ In particular, SAGE recommended that countries considered introducing CYD-TDV only in geographical settings (national or subnational) with high endemicity, as indicated by seroprevalence of approximately >70% in the age group targeted for vaccination or other suitable epidemiologic markers. Pregnancy remains a contraindication.

To date, although licenced in several countries, CYD-TDV has been introduced to the public vaccination programmes of one country alone – the Philippines.

chargé des questions liées à la grossesse. Elles ont également été débattues lors de la Conférence de consensus internationale sur la surveillance harmonisée de la sécurité vaccinale durant la grossesse,⁴ tenue en mars 2016, avant d’être révisées. Le GACVS a examiné cette nouvelle version et convenu qu’une approche mondiale concertée est nécessaire pour parvenir à une harmonisation de la collecte des données sur l’innocuité lors des essais sur les vaccins administrés durant la grossesse.

Il a jugé que les lignes directrices proposées par GAIA étaient utiles et opportunes. Le GACVS a ajouté qu’il serait souhaitable qu’elles prévoient une certaine flexibilité des exigences relatives à la collecte des données de base car dans certains contextes, la collecte de toutes les données indiquées pourrait s’avérer impossible. Il importe de tenir compte des difficultés pouvant exister en termes d’infrastructure, de disponibilité des données de base, d’évolution des taux de base ou des normes cliniques dans divers contextes, ainsi que de reconnaître que la présence des chercheurs pourra parfois avoir une incidence sur les issues de la grossesse. Le GACVS a fait valoir que ces lignes directrices pourront être actualisées et qu’elles pourraient également être appliquées à la surveillance de la sécurité dans le cadre des études d’observation. En outre, pour tester et faciliter leur mise en œuvre, le GACVS a souligné la nécessité de mener des essais et un examen sur le terrain, de mettre au point des outils pratiques à l’usage des chercheurs, d’entreprendre des activités de renforcement des capacités et de formation, et d’élaborer une stratégie de diffusion.

Mise à jour sur le vaccin contre la dengue

Lors de son dernier examen des vaccins contre la dengue, en juin 2015,⁵ le GACVS a étudié les données issues des essais cliniques de Phase III du vaccin CYD-TDV (vaccin tetravalent contre la dengue appelé Dengvaxia, produit par Sanofi Pasteur), notamment les données sur son innocuité à long terme. La surveillance de l’innocuité à court terme des manifestations indésirables les plus courantes a montré que le vaccin est bien toléré. Le GACVS a toutefois noté que le risque d’hospitalisation et de dengue sévère observé chez les enfants de 2 à 5 ans dans la troisième année suivant la vaccination était une source de préoccupation particulière. Il a également recommandé de surveiller le risque de dengue sévère chez les personnes de tous âges qui sont séronégatives avant la vaccination, ainsi que chez les sujets immunodéprimés ou appartenant à une tranche d’âge plus avancée (>45 ans).

En avril 2016, le SAGE a émis des recommandations identifiant les personnes susceptibles de tirer le plus grand avantage de la vaccination par le CYD-TDV et a formulé des orientations générales sur la surveillance post-homologation.⁶ Le SAGE a en particulier recommandé que les pays envisagent une introduction du CYD-TDV uniquement dans les zones géographiques (nationales ou infranationales) de forte endémicité, caractérisées par une séroprévalence d’environ ≥70% dans la tranche d’âge ciblée par la vaccination ou par d’autres marqueurs épidémiologiques adaptés. La grossesse reste une contre-indication.

Bien que le CYD-TDV soit désormais homologué dans plusieurs pays, seules les Philippines l’ont introduit à ce jour dans leur programme public de vaccination. Il y est administré dans le

⁴ The International Alliance for Biological Standardization.

⁵ See No. 34, 2015, pp. 421–423.

⁶ See No. 21, 2016, pp. 282–284.

⁴ The International Alliance for Biological Standardization (IABS).

⁵ Voir N° 34, 2015, p. 421-423.

⁶ Voir N° 21, 2016, p. 282-284.

Here, CYD-TDV vaccination is administered as part of a school-based programme targeting 4th grade children (aged 9–10 years) in 3 highly endemic regions. The first child in the Philippines was vaccinated in April 2016. Currently, approximately 247 820 children are immunized, with a planned total cohort of about 750 000. In this cohort AEFI are monitored through enhanced passive surveillance. All serious AEFI are investigated promptly and reviewed by an independent expert committee. Thus far, 518 AEFIs have been reported including 21 serious AEFIs with 2 deaths. Those included 2 anxiety reactions and 4 cases classified as consistent with a causal association to the vaccine that recovered.

GACVS noted the commitment of the Government of the Philippines, the community and the vaccine and health-care providers in implementing the dengue vaccination programme. The Philippines, as the first country to introduce CYD-TDV vaccination, will thus provide critical post-licensure AEFI surveillance data that will benefit and inform the global community and other jurisdictions.

Representatives of Sanofi Pasteur, the manufacturer of the CYD-TDV vaccine Dengvaxia, gave a presentation to GACVS in which they addressed the longer-term follow-up of hospitalized dengue among Phase III clinical trial participants. With follow-up occurring after 4 years since the first dose of vaccine, no consistent increase was observed in the relative risk of hospitalization or severe dengue in vaccinated individuals aged 9–16 years. However in the younger age group of 2–8 years, an increased relative risk ($RR > 1$, not reaching significance) was observed that declined after 3 years since the first dose. Dengvaxia is not licensed for children aged < 9 years.

Following the introduction of dengue vaccination programmes, GACVS recommends robust, ongoing surveillance with particular emphasis on establishing disease and vaccination history. This requires allocating resources specifically to vaccination registries and ensuring that cases of hospitalized dengue are confirmed in accordance with established case definition. This may be feasible at sentinel sites only. Existing and planned clinical efficacy trials should be evaluated in depth and include careful assessment of pre-immunization seropositivity in selected cohorts. Data from these trials will contribute to a greater understanding of the potential risk factors and underlying immunology of dengue infection and severe dengue post-vaccination.

Proof-of-concept study through multi-country collaboration

In 2011 WHO and partners published the Global Vaccine Safety Blueprint⁷ with the aim of optimizing the safety of vaccines through the effective use of pharmacovigilance principles and methods. An aspect of this was to

cadre d'un programme de vaccination mené en milieu scolaire chez les enfants en 4e année d'école primaire (âgés de 9-10 ans) dans 3 régions fortement endémiques. Le premier enfant a été vacciné aux Philippines en avril 2016 et actuellement, quelque 247 820 enfants ont reçu le vaccin, la cohorte totale ciblée s'élevant à environ 750 000 enfants. Le suivi des MAPI dans cette cohorte est assuré par une surveillance passive renforcée. Toutes les MAPI graves font l'objet d'une enquête rapide et sont examinées par un comité d'experts indépendants. À ce jour, 518 MAPI ont été notifiées, dont 21 MAPI graves et 2 décès. Parmi ces MAPI figuraient 2 réactions anxieuses et 4 cas considérés comme compatibles avec un lien de causalité avec le vaccin, désormais guéris.

Le GACVS a pris bonne note l'engagement du Gouvernement des Philippines, des communautés, des prestataires de soins et des vaccinateurs qui ont participé à la mise en œuvre du programme de vaccination contre la dengue. Étant le premier pays à avoir déployé le CYD-TDV, les Philippines pourront fournir des données cruciales de surveillance post-homologation des MAPI, qui seront d'une grande utilité pour la communauté mondiale et orienteront les décisions d'autres juridictions.

Des représentants de Sanofi Pasteur, le fabricant de Dengvaxia, ont également présenté au GACVS un exposé sur le suivi à plus long terme des cas hospitalisés de dengue parmi les participants des essais cliniques de Phase III. Au terme d'un suivi de plus de 4 ans depuis la première dose de vaccin, aucune augmentation systématique du risque relatif d'hospitalisation ou de dengue sévère n'a été constatée chez les sujets vaccinés de 9 à 16 ans. Toutefois, chez les plus jeunes (2 à 8 ans), on observe un risque relatif accru ($RR > 1$, sans atteindre un niveau significatif), qui redescend après la 3e année suivant la première vaccination. Le Dengvaxia n'est pas homologué pour les enfants de < 9 ans.

Suite à l'introduction des programmes de vaccination contre la dengue, le GACVS recommande d'assurer une surveillance rigoureuse et persistante, en mettant particulièrement l'accent sur la détermination des antécédents de vaccination et de dengue. Cela suppose que des ressources soient spécifiquement allouées à la tenue des registres de vaccination et à l'identification des cas hospitalisés de dengue, conformément à la définition de cas établie. Il se peut que cela ne soit réalisable que sur les sites sentinelles. Les essais présents ou futurs sur l'efficacité thérapeutique devront être évalués de manière approfondie, avec notamment un examen minutieux de la séropositivité avant la vaccination chez certaines cohortes. Les données issues de ces essais contribueront à une meilleure compréhension des facteurs de risque potentiels et des aspects immunologiques sous-jacents de la dengue, voire de la dengue sévère, après la vaccination.

Étude de preuve de concept pour une collaboration multi-pays

En 2011, l'OMS et ses partenaires ont publié le Projet mondial pour la sécurité des vaccins⁷ en vue d'optimiser la sécurité des vaccins en faisant un usage efficace des principes et des méthodes de pharmacovigilance. L'une des composantes de ce projet consis-

⁷ WHO Global Vaccine Safety Blueprint. Available at http://vaccine-safety-training.org/tl_files/vs/pdf/WHO_IVB_12.07_eng.pdf, accessed June 2016.

⁷ WHO Global Vaccine Safety Blueprint. Disponible à l'adresse: http://vaccine-safety-training.org/tl_files/vs/pdf/WHO_IVB_12.07_eng.pdf; consulté en juin 2016.

enhance the capacity for vaccine safety assessment beyond basic pharmacovigilance in LMICs. The Global Vaccine Safety Initiative, jointly with PAHO and VACCINE.GRID,⁸ and through the WHO Secretariat, tested the development of a global network of hospital-based sentinel sites for vaccine safety signal verification and hypothesis testing in LMICs.

A demonstration project was conducted to assess the feasibility, quality and potential for sustainability of a multi-country collaboration for the evaluation of rare vaccine adverse events. The process of setting up the collaboration and conducting a study along with preliminary results were presented to GACVS and complemented by the perspective from one participating institution. A total of 25 hospitals in 16 countries participated in the demonstration project. The project assessed the capacity of the network to verify the known association of measles-containing vaccines and idiopathic thrombocytopenic purpura (ITP) as well as aseptic meningitis associated with the mumps component of some measles/mumps/rubella (MMR) vaccines. The study sites offered training, either in person or by webinars, on the study protocol and study tools and procedures for data collection, local analysis and sharing to a central analysis hub through a secure portal. Case validation was retrospective, based on computer records or log book searches. Following validation, the pooled analysis identified the known ITP association with measles vaccine and the expected association of aseptic meningitis with some MMR vaccines.

GACVS recognized the effort required to successfully perform this complex study. The demonstration project contributed to the development of expertise at many sites involving interested physicians and nurses with GACVS focusing on the questions of sustainability and lessons learned. It is important that the site-specific experience in study implementation, and the collection of quality data, is documented; this will help the conduct of future studies of rare serious health events related to vaccines. In order to accomplish this, WHO must maintain contact with the sites and further communicate with their respective governments to demonstrate the value of this enhanced vaccine safety capacity. Integration of these capacities into the national vaccine pharmacovigilance system would ensure country ownership and sustainability. Sustainability also depends on future funding mechanisms, buy-in from the countries involved and whether there are relevant studies to be conducted. To maintain this expertise, one possibility discussed was to expand beyond vaccine safety to other relevant vaccine studies such as surveillance of vaccine preventable diseases. Following the publication of results from this collaboration, the next steps will be for further work to be carried out on sustainability and identifying relevant future projects. ■

⁸ See <http://www.vaccinegrid.org/public.html>

tait à renforcer la capacité d'évaluation de la sécurité des vaccins au-delà de la pharmacovigilance de base dans les pays à revenu faible ou intermédiaire. L'Initiative mondiale pour la sécurité des vaccins, en collaboration avec l'Organisation panaméricaine de la Santé et VACCINE.GRID,⁸ et au travers de son secrétariat sis à l'OMS, a testé un concept reposant sur la mise en place d'un réseau mondial de sites sentinelles hospitaliers pour la vérification des signaux de sécurité des vaccins et la mise à l'essai des hypothèses dans les pays à revenu faible ou intermédiaire.

Un projet pilote a été réalisé pour évaluer la faisabilité, la qualité et la pérennité potentielle d'une collaboration multi-pays visant à étudier les manifestations postvaccinales indésirables rares. Le processus utilisé pour établir cette collaboration et conduire une étude a été présenté au GACVS, de même que les résultats préliminaires. Cet exposé a été complété par la perspective offerte par l'une des institutions participantes. En tout, 25 hôpitaux dans 16 pays ont participé au projet pilote. Le projet visait à évaluer la capacité du réseau à vérifier l'association connue entre les vaccins à valence rougeole et le purpura thrombopénique idiopathique (PTI), ainsi que la méningite à liquide clair associée à la composante antiourlienne de certains vaccins antirougeoleux-antiourlien-antirubéoleux (ROR). Les sites inclus dans l'étude ont bénéficié d'une formation, en personne ou en ligne, sur le protocole de l'étude, ainsi que sur les outils et procédures de collecte, d'analyse locale et de transfert des données vers une plateforme d'analyse centralisée au moyen d'un portail sécurisé. La validation des cas était rétrospective, reposant sur une recherche des dossiers ou registres informatiques. Après la validation, la méta-analyse est parvenue à identifier l'association connue entre le PTI et le vaccin anti-rougeoleux, ainsi que l'association escomptée entre la méningite à liquide clair et certains vaccins ROR.

Le GACVS a salué les efforts déployés pour mener à bien cette étude complexe. Il a ajouté que ce projet pilote contribuera à améliorer le savoir-faire sur de nombreux sites où travaillent des médecins et des infirmiers intéressés en la matière. Le GACVS a mis l'accent sur les questions de pérennité et les enseignements tirés de cette collaboration. Il est important qu'au niveau de chaque site, l'expérience faite de l'étude et de la collecte de données de qualité soit consignée pour guider la réalisation de futures études sur les manifestations graves et rares associées à la vaccination. À cet effet, il convient que l'OMS demeure en contact avec les sites et continue de communiquer avec les gouvernements respectifs correspondants afin de démontrer les bénéfices de cette capacité améliorée d'évaluation de la sécurité des vaccins. L'intégration de ces capacités dans le système national de pharmacovigilance vaccinale permettrait de garantir l'adhésion des pays et la pérennité de cet effort. Cette pérennité dépendra également des futurs mécanismes de financement, de l'engagement des pays eux-mêmes et de l'existence d'études pertinentes à entreprendre. Pour préserver ce savoir-faire, l'une des possibilités évoquées serait d'étendre cette initiative au-delà des seules questions de sécurité des vaccins pour inclure d'autres études appropriées sur les vaccins, comme la surveillance des maladies évitables par la vaccination. Après la publication des résultats issus de cette collaboration, les prochaines étapes consisteront à approfondir la réflexion sur les moyens de pérenniser cet effort et à identifier des projets futurs adaptés. ■

⁸ Voir <http://www.vaccinegrid.org/public.html>

**Statements by
WHO Global Advisory
Committee on Vaccine Safety
on the safety of human
papillomavirus (HPV) vaccines
2013–2016**



**World Health
Organization**

GACVS Safety update on HPV Vaccines

Geneva, 13 June 2013

At its meeting on 13 June 2013, GACVS reviewed updated information about the safety of HPV vaccines. The last review was conducted in June 2009. GACVS noted at the time that accumulating evidence on the safety of HPV vaccines was reassuring and that studies on HPV immunization had been initiated, along with capacity-building for adverse events monitoring. GACVS places a high priority on the ongoing collection of high-quality safety data in settings where the vaccine is being introduced.

In the past 4 years, safety data continued to accumulate as countries have initiated or expanded their immunization programs. The GAVI Alliance has also begun taking steps to make HPV vaccine available to women in developing countries where the burden of cervical cancer is considerable. To date, some 175 million doses of HPV vaccines have been distributed. A review of adverse events reported to the US Vaccine Adverse Event Reporting System following the distribution of over 23 million doses was published in 2009 (Slade 2009). Many countries where HPV is licensed now have considerable post-marketing data and no concerns have been identified. The manufacturers of currently available vaccines have developed pregnancy registries and are maintaining long term safety studies in conjunction with efficacy.

The Committee reviewed data from the United States, Australia, Japan and the manufacturers of Cervarix® (GlaxoSmithKline) and Gardasil® (Merck). Updates from the United States included an extension of the spontaneous reports to VAERS since the published review in 2009 as well as completed and planned studies from the Vaccine Safety Datalink. In Australia a new program targeting males started in February 2013 and data are just becoming available.

Data from all sources continue to be reassuring about the safety of the two vaccines. The data from VAERS now includes over 50 million doses distributed since 2006 and the profile has not changed significantly since the review in 2009. Reported adverse events not identified at the time of the first review, namely syncope and venous thromboembolism (VTE), were further investigated. For syncope, it continues to be reported but remains an event with a plausible relationship given the population and settings under which HPV vaccine is given. Adherence to a 15-minute observation period following vaccination has thus been strengthened as a recommendation. For VTE, while a rapid cycle analysis in the VSD did not find an increased risk, this is further being investigated with appropriate control for confounders such as oral contraceptive use, smoking and other risk factors in this population. Similarly, the VSD did not find any increased risk of Guillain-Barré syndrome or stroke.

In Australia, safety surveillance has been enhanced and the expert group continues to look at reported events. To date, with almost 7 million doses distributed, the previously investigated concern regarding an increased incidence of anaphylaxis was not confirmed. Following the extension of the vaccination program in males and enhanced surveillance since February 1 2013, preliminary results show the safety profile of Gardasil as similar to the profile among females.

The experience in Australia also provides useful lessons for countries introducing new vaccines in this age group, especially when vaccines are administered in a school based vaccination settings. In May 2007, soon after the introduction of the school-based program, 26 of 720 girls vaccinated at a girls' school developed symptoms including dizziness, palpitations, syncope or collapse, weakness, and aphasia. Four were transported by ambulance to hospital where further clinical evaluation found no organic basis for the reported symptoms. This cluster of adverse events was determined to be a result of a psychogenic response to vaccination. The event generated substantial media interest and public concern in Australia. (Buttery 2008, Gold 2010). Such cases require a prompt and thorough medical evaluation to establish a diagnosis and then an assessment of the relationship, if any, to the vaccine or vaccination as well as a proactive approach to communication, employing risk communication principles.

Surveillance from the two manufacturers found no signals that suggest a need for revisions to product labelling. Both have maintained surveillance of pregnancy outcomes following inadvertent vaccination during pregnancy. Detailed analyses of results have not found any new adverse outcomes related to HPV vaccination. For Gardasil, long term follow-up has now extended to over 8 years in the longest cohort, and no significant increase in newly diagnosed health events have been identified among those vaccinees. Updated analyses of the pregnancy registry have also been reassuring in that no adverse pregnancy outcomes have been observed beyond background expected rates. For Cervarix, the data have been similarly reassuring regarding pregnancy outcomes and specific events of interest such as immune mediated diseases. Risk of syncope and anaphylaxis have been added to the label to warn of these potential events, the former being also possibly related to conditions around the vaccination experience itself.

Finally, cases of complex regional pain syndrome (CPRS) were reported from Japan where over 8 million doses of HPV vaccines have been distributed. CPRS is a painful condition that emerges in a limb usually following trauma. Cases have been reported following injury or surgical procedures. It remains of unknown etiology and may occur in the absence of any documented injury. CPRS following HPV vaccines has received media attention in Japan with 5 reported cases most of which seem not compatible with typical CPRS cases. Review by an expert advisory committee could not ascertain a causal relationship to vaccination given lack of sufficient case information and in many cases could not reach a definitive diagnosis. While these are under investigation, Japan has continued to provide HPV vaccine in their national program.

In summary, 4 years after the last review of HPV vaccine safety and with more than 170 million doses distributed worldwide and more countries offering the vaccine through national immunization programs, the Committee continues to be reassured by the safety profile of the available products. Anaphylaxis and syncope, outcomes previously identified as concerns, have been addressed through further studies and appropriate revisions were made to the products labeling. Serious adverse events that have been reported as potential signals have been investigated in more detail, including Guillain-Barre Syndrome, seizures, stroke, venous thromboembolism, anaphylaxis, and other allergic reactions – many using rapid cycle analysis in the VSD in the United States. Surveillance of pregnancy outcomes among women inadvertently vaccinated during pregnancy through spontaneous reports and registries have not detected any adverse outcomes above expected rates.

The cases of chronic pain being reported from Japan deserve specific mention. To date there is little reason to suspect the HPV vaccine, given its growing use worldwide in the absence of a similar signal from elsewhere. Recognizing the public concerns voiced, the Committee urges careful documentation of each case and a thorough search for a definitive diagnosis by medical specialists in order to best guide treatment. A timely clinical assessment and diagnosis of each case followed by appropriate treatment is therefore essential.

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GACVS Safety update on HPV Vaccines

Geneva, 17 December, 2013

At its meeting on 12 December 2013, GACVS reviewed evidence related to autoimmune disease and the HPV vaccine, with a focus on multiple sclerosis (MS). The last review was conducted in June 2013, where the Committee reviewed updated data from the United States, Australia, Japan and the manufacturers of Cervarix® (GlaxoSmithKline) and Gardasil® (Merck). With >175 million doses distributed worldwide and more countries offering the vaccine through national immunization programmes, the Committee continued to be reassured by the safety profile of the available products. Serious adverse events that have been reported as potential signals have been investigated in more detail and were not confirmed, including Guillain-Barré syndrome, seizures, stroke, venous thromboembolism, anaphylaxis and other allergic reactions. Surveillance of pregnancy outcomes among women inadvertently vaccinated during pregnancy through spontaneous reports and registries have not detected any adverse outcomes above expected rates.

While surveillance data and epidemiologic studies on HPV vaccine have continued to reassure, allegations have continued to surface in the media and elsewhere about the safety of the vaccine. Epidemiologic studies before and after licensure showed no increased risk of autoimmune disease, including MS. All along, such diseases have been under particularly careful investigation given their correspondingly high age-specific background incidence[1-3].

Examples of such studies include a register-based cohort study in Sweden and Finland that included almost 1 million girls aged 10-17 years, among whom close to 300,000 were vaccinated against HPV[4]. The study investigated whether vaccination was associated with an increased risk of autoimmune, neurological and thromboembolic events. The study results did not show evidence supporting associations between exposure to HPV vaccine and autoimmune, neurological, and venous thromboembolic adverse events.

In the U.S., an observational study involving close to 200,000 girls and young women who had received at least one dose of HPV vaccine found no increased incidence of 16 investigated autoimmune diseases in the vaccinated compared to the non-vaccinated group[5]. The incidence of MS in the vaccinated cohort, for example, was not significantly higher than the non-vaccinated cohort (incidence rate ratio 1.37, 95% confidence interval 0.74 to 3.20). In a third study, a pooled analysis of data from 11 clinical trials involving nearly 30,000 participants over 10 years of age, of which 16,142 received at least one dose of Cervarix ® and 13,811 received either a placebo containing aluminum hydroxide or one of 2 different hepatitis A vaccines. No increased risk for the onset of autoimmune diseases after administration of Cervarix ® was observed in comparison to the control group[6].

The committee was provided with an overview of cases that were the subject of concern in France. These included one case of MS that had been adjudicated by a French Regional Commission for Conciliation and Compensation (CRCI). Another 14 cases of MS were reported through regional pharmacovigilance centres and/or the manufacturers to the European Medicines Agency. All 15 cases had been classified of “doubtful” causality, according to the French grading system[7].

In addition, the overview from France included results of a cohort study involving 2 million girls aged 12 to 16 showing a lack of increase in hospitalization rates for auto-immune diseases among those who received the HPV vaccine (2.1/10,000 patients/year) compared to those who did not (2.09/10,000 patients/year).

In summary, GACVS was presented with a series of cases of adverse events following the HPV vaccine. Multiple studies have demonstrated no increase in risk of autoimmune diseases, including MS, among girls who received HPV vaccine compared to those who had not. The Committee continues to be reassured by the safety profile of the vaccine, but notes the importance of continued surveillance and epidemiological investigation with an emphasis on the collection of high quality data; such data are essential for interpreting adverse events which occur following vaccination. Allegations of harm from vaccination based on incomplete information can lead to real harm when, as a result, effective vaccines are not used.

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March 12, 2014

**Global Advisory Committee on Vaccine Safety
Statement on the continued safety of HPV vaccination**

As with all new vaccines, the Global Advisory Committee on Vaccine Safety has been reviewing the safety of HPV vaccines since they were first licensed in 2006. The World Health Organization (WHO) recommends the introduction of HPV vaccination into national immunization programmes where prevention of cervical cancer is a public health priority and the introduction is programmatically feasible [1]. While early detection of pre- and cancerous cells through screening programs has helped decrease incidence rates of cervical cancer in women aged 25-45 in the UK, for example [2], that decrease has plateaued in the past decade. While safety concerns about HPV vaccines have been raised, these have systematically been investigated: to date, the GACVS has not found any safety issue that would alter any of the current recommendations for the use of the vaccine.

The purpose of this update is to summarize the work of GACVS over the past six years in reviewing the safety of HPV vaccines. It is important to highlight and reiterate this work because a number of national immunization programs have been facing real and potential public losses of confidence in their programs as a result of increased negative publicity, even from safety issues that have been addressed.

To date, the GAVCS has reviewed evidence related to syncope, anaphylaxis, venous thromboembolism, adverse pregnancy outcomes, Guillain Barre Syndrome, and stroke [3]. It also examined concerns around the aluminium adjuvant used in HPV vaccines, with considerations around the toxicology of aluminium adjuvants and studies by investigators claiming that aluminium in the quantities used in vaccines are associated with adverse health outcomes [4]. Finally the Committee also reviewed the question of autoimmune disease, specifically around multiple sclerosis (MS), cerebral vasculitis, and an evolving concern over cases of complex regional pain syndrome (CRPS) and/or other chronic pain conditions following vaccination that have surfaced.

With respect to aluminium, the GACVS has had occasion to review the safety of the adjuvant on several occasions, beginning in 1999. At that time, deltoid muscle biopsies performed in France on a number of patients with a variety of complaints revealed in a small number the presence of a minute inflammatory focus of macrophages with associated necrosis. These localized lesions, called macrophagic myofasciitis (MMF), have been shown to contain aluminium salts [5, 6]. Since the location of the lesions in the deltoid muscle coincides with the usual site of injection for vaccines, these microscopic lesions may appear to be related to immunization. The investigators from the "Groupe d'études et de recherche sur les maladies musculaires acquises et dysimmunitaires" (GERMAAD) have suggested that vaccination and localized MMF lesions might be associated with a multi-system disorder. The GACVS has reviewed evidence regarding MMF on several occasions since that time and continues to reaffirm that, while MMF is clearly linked to a vaccination "tattoo" among some patients who have received an aluminium containing vaccine, the associated systemic symptoms related to that finding have never been scientifically proven. Statements about MMF were published in 1999, 2002 and 2004 [4]. While there have never been any published reports of MMF in recipients of HPV vaccines, there is no plausible reason to suspect that any reports of MMF would be associated with systemic symptoms following aluminium containing HPV vaccines any more than the finding of the histological lesion of MMF following hepatitis B vaccine and clinical symptoms.

In 2012, the GACVS reviewed two studies claiming an association between aluminium in vaccines and autism spectrum disorder [7, 8]. It found serious flaws in the two studies that limited their value even for hypothesis generation. In December 2013, the GACVS reviewed evidence related to HPV vaccine and

autoimmune disease, specifically multiple sclerosis [3]. While there remain case reports in the literature, multiple epidemiologic studies have not demonstrated any increased risk of autoimmune diseases, including MS, in studies, some of which have included girls who have received HPV vaccine compared to those who had not [9, 10, 11, 12].

Several papers have also been published pertaining to the finding of HPV L1 gene DNA fragments in clinical specimens following HPV vaccination [13, 14]. These papers claimed an association with clinical events of an inflammatory nature, including cerebral vasculitis. While the GACVS has not formally reviewed this work, both the finding of DNA fragments in the HPV vaccine and their postulated relationship to clinical symptoms, have been reviewed by panels of experts. First, the presence of HPV DNA fragments has been addressed by vaccine regulatory authorities who have clearly outlined it as an expected finding given the manufacturing process, and not a safety concern [15]. Second, the case reports [13] of adverse events hypothesized to represent a causal association between the HPV L1 gene DNA fragments and death were flawed in both clinical and laboratory methodology [16]. The paper described 2 fatal cases of sudden death in young women following HPV vaccine, one after 10 days and one after 6 months, with no autopsy findings to support death as result of cerebral vasculitis or an inflammatory syndrome. Thus the hypotheses raised in these papers are not supported by what is understood about the residual DNA fragments left over following vaccine production [17]: given the extremely small quantities of residual HPV DNA in the vaccine, and no evidence of inflammation on autopsy, ascribing a diagnosis of cerebral vasculitis and suggesting it may have caused death is unfounded.

In June 2013, the GACVS reviewed the concerns arising in Japan in regard to reports described as CRPS in a few cases, and other chronic pain conditions following HPV vaccine. At the time, GACVS found no evidence to suggest a causal link with the HPV vaccine, and recommended careful documentation of each case and definition of diagnostic criteria to guide management and causality assessment. The Committee has meanwhile continued to monitor the HPV vaccine and considered further issues during their meeting in December 2013 [3]. In Japan, an expert advisory committee has continued to meet and review the situation but has not yet reached a conclusion. It is acknowledged that the HPV vaccine may be a more painful injection, leading to frequent complaints of pain, which, in some settings, may trigger additional non-specific complaints [18, 19]. As to Complex Regional Pain Syndrome, this entity has been described following various forms of trauma, including injury, surgical procedures and injections. It is therefore plausible that CRPS could develop following the injection of any vaccine (however, such cases have been very rarely described in the literature [20]).

In summary, the GACVS continues to closely monitor the safety of HPV vaccines and, based on a careful examination of the available evidence, continues to affirm that its benefit-risk profile remains favorable. The Committee is concerned, however, by the claims of harm that are being raised on the basis of anecdotal observations and reports in the absence of biological or epidemiological substantiation. While the reporting of adverse events following immunization by the public and health care providers should be encouraged and remains the cornerstone of safety surveillance, their interpretation requires due diligence and great care. As stated before, allegations of harm from vaccination based on weak evidence can lead to real harm when, as a result, safe and effective vaccines cease to be used. To date, there is no scientific evidence that aluminium-containing vaccines cause harm, that the presence of aluminium at the injection site (the MMF “tattoo”) is related to any autoimmune syndrome, and that HPV DNA fragments are responsible for inflammation, cerebral vasculitis or other immune-mediated phenomena.

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Global Advisory Committee on Vaccine safety

Statement on Safety of HPV vaccines

17 December 2015

Since first being licensed at the beginning of 2006, more than 200 million doses of HPV vaccines have been distributed globally. The World Health Organization (WHO) recommends that HPV vaccines be introduced into national immunization programmes provided that: prevention of cervical cancer and/or other HPV-related diseases constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost-effectiveness of vaccination strategies in the country or region is considered¹. The GACVS has systematically investigated safety concerns raised about HPV vaccines and has issued several reports in this regard². To date, it has not found any safety issue that would alter its recommendations for the use of the vaccine.

GACVS reviewed data from a recent retrospective cohort study from the French National Agency for Medicines and Health Products Safety on autoimmune conditions following HPV vaccination³. This large study of over 2 million girls showed a similar incidence in the vaccinated and unvaccinated populations for all conditions studied with the exception of Guillain-Barre syndrome where an increased risk was identified, mainly focused within 3 months after vaccination. This risk in the first few months after vaccination was very small (~1 per 100,000 vaccinated children) and has not been seen in other smaller studies. Additional studies in adequately sized populations will help evaluate this finding and, if confirmed, better

¹ See no. 43, 2014, PP. 465–492.

² See http://www.who.int/vaccine_safety/committee/topics/hpv/en/

³ Agence nationale de sécurité des médicaments et des produits de santé. Vaccins anti-HPV et risque de maladies autoimmunes : étude pharmacoépidémiologique. http://ansm.sante.fr/content/download/80841/1023043/version/1/file/Ansm_Gardasil-Hpv2_Rapport_Septembre-2015.pdf

assess the magnitude of an eventual risk. This risk – small, if it exists at all – needs to be seen in the context of the long-lasting cancer-prevention benefits of HPV infection.

As well, concerns about complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) following HPV vaccination have been raised in certain geographic locations. These are both disorders of unclear and possibly heterogeneous etiology and the epidemiology of both conditions is not well characterized. CRPS is a chronic, painful condition usually affecting a single limb that typically follows an episode of trauma or immobilisation of a limb. The onset of symptoms of CRPS is difficult to define and is usually recognised among patients with continuing pain long after the trauma.

POTS is characterized by an abnormally large and sustained increase in heart rate when changing from a lying down to an upright position. This excessive heart rate increase is usually accompanied by a range of symptoms of orthostatic intolerance. Several clinical and epidemiological features contribute to POTS being especially challenging to study. Onset of POTS may be extremely difficult to ascertain retrospectively. POTS is probably relatively common in young adolescents, may be relatively infrequently diagnosed, and may be difficult to distinguish from the normal range of physiologic responses in this age group. Additionally, syncope is a common adverse event in response to immunization, especially among adolescents, which may lead to differential ascertainment of POTS in vaccinated and unvaccinated populations. In spite of the difficulties in diagnosing or fully characterizing these syndromes, review of pre- and post-licensure data provide no evidence that these syndromes are associated with HPV vaccination. Some symptoms of CRPS and POTS also overlap with symptoms of chronic fatigue syndrome (CFS) for which a published observational study reported no association with HPV vaccines⁴.

Although some cases of POTS reports were severe and long-lasting, the prognosis of POTS with symptomatic management is usually favourable, and symptoms in adolescents often resolve over time. Given the lack of specificity of some of the symptoms reported following HPV

⁴ Donegan K, Beau-Lejdstrom R, King B, et al. Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. *Vaccine* 2013; 31:4961-7.

vaccination, clinicians are encouraged to refer severely-affected patients to physicians familiar with these syndromes for diagnosis and management. Prompt diagnosis and management by experienced clinicians may avoid harmful and unnecessary medical interventions and promote a prompt return to normal activities.

The circumstances in Japan, where the occurrence of chronic pain and other symptoms in some vaccine recipients has led to suspension of the proactive recommendation for routine use of vaccine in the national immunization program, warrants additional comment. Review of clinical data by the national expert committee led to a conclusion that symptoms were not related to the vaccine, but it has not been possible to reach consensus to resume HPV vaccination. As a result, young women are being left vulnerable to HPV-related cancers that otherwise could be prevented. As GACVS has noted previously, policy decisions based on weak evidence, leading to lack of use of safe and effective vaccines, can result in real harm⁵.

Continued pharmacovigilance will be important in order to ensure that concerns related to the use of HPV vaccines can be addressed with the best possible evidence. The impact of HPV vaccines on HPV-related clinical outcomes, including precancerous lesions is well established. The greatest health benefit globally is anticipated in countries without routine cervical cancer screening, where the vaccine is yet to be introduced. Enhanced spontaneous reporting of adverse events following immunisation should be put in place to ensure that those who could benefit the most from the intervention are vaccinated with adequate safety monitoring.

⁵ http://www.who.int/vaccine_safety/committee/topics/hpv/GACVS_Statement_HP_V12_Mar_2014.pdf

Report from the World Health Organization's Third Product Development for Vaccines Advisory Committee (PDVAC) meeting, Geneva, 8-10th June 2016

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Abstract

The third meeting of WHO's Product Development for Vaccines Advisory Committee (PDVAC) was held in June 2016, with a remit to revisit the pathogen areas for which significant progress has occurred since recommendations from the 2015 meeting, as well as to consider new advances in the development of vaccines against other pathogens. Since the previous meeting, significant progress has been made with regulatory approvals of the first malaria and dengue vaccines, and the first phase III trials of a respiratory syncytial virus (RSV) vaccine candidate has started in the elderly and pregnant women. In addition, PDVAC has also supported vaccine development efforts against important emerging pathogens, including Middle Eastern Coronavirus (MERS CoV) and Zika virus. Trials of HIV and tuberculosis vaccine candidates are steadily progressing towards pivotal data points, and the leading Norovirus vaccine candidate has entered a Phase IIb efficacy study. WHO's Immunization, Vaccine and Biologicals (IVB) department is actively working in several pathogen areas on the recommendation of PDVAC, as well as continuing horizon scanning for advances in the development of vaccines that may benefit low and middle income countries, such as the recent licensure of the enterovirus 71 (EV71) vaccine in China. Following on from discussions with WHO's Strategic Advisory Group of Experts (SAGE) on Immunization, PDVAC will also look beyond licensure and consider data needs for vaccine recommendation and implementation to reduce the delay between vaccine approval and vaccine impact.

Context

WHO's PDVAC was established by the Department of Immunization, Vaccines and Biologicals (IVB) in 2014, following a review of WHO's process for strategic priority setting for vaccines. The need for a group to advise WHO specifically on vaccine product development was highlighted, to accelerate vaccine availability and ensure accessibility of vaccines to low and middle income countries (LMICs). PDVAC's remit is to advise on the product development strategy of vaccine candidates at Phase 2 of clinical evaluation or earlier and to report its proceedings to the WHO's principal committee on immunization policy recommendations: the Strategic Advisory Group of Experts on Immunization (SAGE). The PDVAC committee has a critical role in assessing the evolving vaccine development landscape and in helping to define where and how WHO can be most impactful, according to three criteria:

- Unmet public health need for a vaccine focusing on the LMIC perspective,
- Likelihood of a product emerging from the pipeline, as defined by probability of technical and regulatory success, and the extent of awareness, activity and investment in given area,
- A clear role for WHO with perceived added value for engagement in the pathogen area

Typically WHO engages in a pathogen area by working with a broad set of key vaccine development stakeholders to develop consensus on pivotal clinical trial design, vaccine roadmaps, or guidance documents on desired vaccine properties, referred to as Preferred Product Characteristics (PPCs). PPCs define WHO preferences for the properties of vaccines to be used in LMICs that are 5-10 years from licensure, and inform target product profiles in use by manufacturers and funders for vaccines. PDVAC also encourages developers to be aware of the process and requirements for WHO prequalification (PQ). WHO Prequalification is a service to UNICEF and other UN agencies that purchase vaccines once they have been licensed, to determine the acceptability, in principle, of vaccines from different sources for supply to these agencies. It aims to ensure that diagnostics, medicines, vaccines and immunization-related equipment and devices for high burden diseases meet global standards of quality, safety and efficacy, and are appropriate for use in LMICs contexts in order to optimize the potential benefit of these interventions¹.

Vaccine product development milestones since the 2015 PDVAC meeting

The third PDVAC meeting was held in Geneva from 8-10th June 2016. Dr Jean-Marie Okwo-Bele, director of IVB, opened proceedings with a synopsis of the significant milestones in vaccine development in the nine months since the previous meeting in September 2015:

- the first dengue and malaria vaccines have been licensed or achieved the equivalent of licensure, respectively,
- the first RSV vaccine candidate has entered phase III studies in the elderly and pregnant women,
- the most advanced HIV vaccine candidate has met its endpoints in the interim analysis of a Phase II study, and preparations to commence an efficacy study are underway,
- WHO convened the MERS-Coronavirus R&D community, and a Phase 1 clinical study is now underway (NCT02670187),
- Ebola virus vaccines are under review for WHO Emergency Use Assessment and Listing (EUAL) and have progressed to the point of consideration for licensure in record time ,
- the Zika virus outbreak has been declared a Public Emergency of International Concern (PHEIC), and there are co-ordinated efforts to develop a vaccine as expeditiously as possible. PDVAC is contributing significantly through a PDVAC working group which has overseen the development of a Zika virus vaccine target product profile (TPP), and developed regulatory considerations towards phase I and emergency use authorization.

In addition to these significant advances in vaccine development, the UK government published in May 2016 the report on 'Tackling Drug-Resistant Infections Globally' it commissioned in collaboration with the Wellcome Trust². The report highlights the urgent need to reduce reliance on currently available antimicrobials, without which today's 700,000 deaths per year from drug resistant microbes is forecast to increase to 10 million, by 2050. The cost in terms of lost global production due to infections that are not controllable due to antimicrobial resistance (AMR) is estimated to be \$100 trillion by 2050 if no action is taken². The development of vaccines against pathogens that are

currently controlled by antimicrobials has become an imperative, as they have the potential to reduce the prevalence and spread of drug resistance, as well as to reduce the use of antimicrobials more broadly³.

The Decade for Vaccines' Global Vaccine Action Plan (GVAP) is approaching its mid-term review, requiring an assessment of progress against objectives since its inception in 2011, and strategic planning to achieve the stated targets with in the remaining 5 years. Part of PDVAC's remit is to review the vaccine development pipeline and consider the priority activities for IVB, within this context. During the remaining timeframe, a number of vaccines could reach licensure, and WHO needs to ensure early engagement with policy makers regarding potential vaccine implementation, as well as alignment with GAVI's Vaccine Investment Strategy.

To facilitate information sharing, and tracking of progress within the global vaccine development community, the WHO has established and maintains an online 'Vaccine Pipeline Tracker' in which information regarding all current clinical studies in several different pathogen areas can be found⁴. In addition, landscape analyses for 25 pathogens from the 2015 meeting have been collated within a special issue of the journal 'Vaccine' and all are available through open access⁵. These documents are authored by independent subject matter experts and review the status of vaccine candidate development, as well as assessing possible pathways to regulatory approval.

Recommendations for PDVAC following Oct 2015 and April 2016 SAGE meetings

PDVAC reports progress on the global vaccine development pipeline to WHO's Strategic Advisory Group of Experts (SAGE) on Immunization. At the most recent meeting in April 2016, advances in the development of interventions (vaccines and monoclonal antibodies) for Respiratory Syncytial Virus (RSV) were presented for information. The reports from both SAGE meetings are available online^{6,7}.

Much of the discussion focused on the increasing need for implementation science, as well as safety and efficacy data to support the assessment of a vaccine for policy recommendation. As emerging vaccines are likely to require new vaccination platforms, such as maternal immunization, or visits outside of the current vaccination schedule, such as for the recently licensed malaria vaccine RTS,S, cost-effectiveness data informing their optimal use and potential impact must be generated in line with conventional clinical data required for regulatory approval, to minimise the delay between vaccine licensure and uptake⁸.

The scope and objectives of the 2016 PDVAC meeting

The goals of this third PDVAC meeting were to revisit the pathogen areas where there has been significant progress to report since recommendations from the 2015 meeting, as well as to:

- Review status of vaccine development in 7 new pathogen areas where there has been significant vaccine development progress, or where there is significant disease burden but R&D has stalled,
- Refine the workplan and strategic directions for IVB in specific pathogen areas,
- Identify cross-cutting issues that accelerate vaccine development or prepare for policy decisions,
- Where appropriate, consider how to better align PDVAC's vaccine development activities and strategies with other areas of research,
- To inform the vaccine development community regarding steps beyond vaccine licensure, and WHO processes for vaccine policy recommendation.

Vaccine development status and PDVAC recommendations, by pathogen

1. The Global Vaccine Action Plan (GVAP): progress towards malaria, HIV, tuberculosis and improved influenza vaccines

The GVAP is a 10-year strategic framework derived from the Decade of Vaccines Collaboration⁹ to prevent millions of deaths by 2020 through more equitable access to existing vaccines for people in all communities. Within this framework is a specific objective that supports research and development of innovations that will maximise the benefits of immunization, with indicators for progress towards development of HIV, malaria, tuberculosis and influenza vaccines. The GVAP is currently at its mid-term review stage, and following the 2015 recommendation

from SAGE¹⁰, the 2016 GVAP assessment will highlight advances made in these areas. These four pathogen areas are standing agenda items for discussion at PDVAC.

1.1 Tuberculosis

In 2014, *Mycobacterium tuberculosis* (Mtb) killed 1.5 million people (of whom 0.4 million were co-infected with HIV) and is now the world's most deadly infectious disease¹¹. Approximately 480,000 cases/annum are multi-drug resistant (MDR) or extensively drug resistant (XDR) and some strains are untreatable. In 2014, six million new cases of Mtb were reported to WHO, fewer than two-thirds (63%) of the 9.6 million people estimated to have contracted the disease. This means that 37% of new cases were not detected or reported. A vaccine is imperative to achieving the End TB goals¹², particularly through reaching the population who are undiagnosed and continue transmitting disease. As such, the TB vaccine development community has turned its focus to the development of vaccines targeted to adolescents and adults as the major source of Mtb transmission. Modelling studies suggest that prevention of pulmonary disease in this population from primary infection and from reinfection or reactivation of existing infections is the most effective strategy to prevent Mtb infection and disease in infants and children¹³. The most advanced vaccine candidates are targeting this indication, including current neonatal BCG replacement strategies that are also undergoing evaluation as a booster in later life. Several of these candidates are in proof-of-concept clinical studies and are approaching key endpoints through prevention of infection or disease, or prevention of disease due to reinfection in these target populations in the next 12-24 months¹⁴. With this in mind, PDVAC recommended that WHO prioritize and facilitate consensus building with respect to the development of strategic goal(s) and PPC(s) for vaccines targeted to adolescents and adults, in the first instance. There are several candidates and platforms in the pipeline targeting this goal in this population, and other important target populations⁴ and PDVAC acknowledged the significant need for development for these vaccines in parallel, as well as continued efforts to understand the biological mechanism of disease to support the immunological rationalization of candidates.

1.2 HIV

The Pox-Protein Public Private Partnership (P5) consisting of Sanofi, GlaxoSmithKline (GSK), Bill & Melinda Gates Foundation, the US Military HIV Research Program (MHRP), and the HIV Vaccine Trials Network (HVTN) have been collaborating with the US National Institutes of Allergy and Infectious Disease (NIAID) to optimise and assess the efficacy of the ALVAC/heterologous prime boost approach, following the demonstration of partial efficacy in the RC144 trial in Thailand¹⁵. The interim data from a phase I/II study (HVTN 100) met its humoral and cellular immunological 'go' criteria, exceeding the RV144 responses against sub-Saharan clade C antigens. Extrapolation of these responses to those observed with RV144, suggest that the optimised vaccine could offer at least 50% protection following a 12 month booster. Based on these data, a randomised placebo controlled phase IIb/III efficacy trial (HVTN702) enrolling 5,400 subjects will be initiated in late 2016 in South Africa, and will evaluate ALVAC (clade C) prime/bivalent recombinant gp120 protein with MF59 adjuvant as a heterologous boost, as well as the effect of a booster at 12 months¹⁷. Futility analyses will be undertaken early in the 2 year follow-up period. Correlate of protection studies and assessment of cross-reactivity to other regional clades are included in the study design. Discussions with the South African Medicines Control Council (MCC) are ongoing, and licensure in South Africa could be as early as 2021.

Other vaccine candidates are in development, including Janssen's heterologous prime boost approach with Ad26/gp140, currently undergoing dose regimen selection in phase I/IIa trials.

Antibody-mediated prevention using broadly neutralizing, potent monoclonal antibody (bnMAbs) approaches are also undergoing Phase I/IIa clinical evaluation. The NIAID/Vaccine Research Centre's VRC01 broadly neutralising MAb is the most advanced candidate which has been shown to neutralise CD4 binding of 90% of viral isolates. HVTN 703 is a phase IIb study to evaluate the efficacy of VRC01 in reducing acquisition of HIV-1 infection in high risk populations in the Americas and sub-Saharan Africa, and started enrolment in 2016. If shown to be effective, administration of VRC01 could be positioned as a single dose supplement to increase effectiveness of anti-retrovirals.

PDVAC commended the advances in HIV vaccine development, and requested to be kept informed about progress with HVTN702. Currently, there are no known intentions for global studies with the P5 candidate vaccine, or to seek

WHO prequalification. PDVAC encourages the P5 partners and the South African HIV vaccine development community to keep WHO fully informed about progress with the trial. Concerns were expressed regarding the lack of follow-on studies in Thailand, given that the initial landmark RV144 trial was performed there.

1.3 Malaria

Despite the substantial reduction over the last 15 years (over 50% for global malaria mortality in children aged <5 years), mainly due to greater investments in malaria control, the WHO estimates there were 214 million malaria cases in 2015, 88% of these in Africa. Of the 438,000 people who died from the disease in 2015, 90% reside in Africa¹⁷. Given the increase in multi-drug and insecticide resistance, there remains an urgent need for a vaccine to combat malaria.

As reported in the 2015 PDVAC meeting summary¹⁸, the European Medicine's Agency (EMA) provided a positive scientific opinion, indicating a favorable assessment of the risk-benefit balance of RTS,S/AS01 from a regulatory perspective. In October 2015, two advisory bodies to WHO, namely SAGE and the Malaria Policy Advisory Committee (MPAC), recommended pilot implementation studies of the 4-dose schedule of the RTS,S/AS01 vaccine in 3–5 distinct epidemiological settings in sub-Saharan Africa, at sub-national level, covering moderate-to-high transmission settings, with three doses administered to children between 5 and 9 months of age, followed by a fourth dose 15–18 months later. The intent of these pilot studies is to assess:

- the feasibility of providing all four doses of RTS,S to the target age group through existing health services;
- the impact of RTS,S on child mortality;
- whether there are any safety issues, particularly evidence of any causal relationships between RTS,S administration and either meningitis or cerebral malaria (both signalled in the phase III trials),
- whether introduction of the vaccine impacts positively or negatively on existing country immunization programs and on the use of currently recommended malaria control measures.

Discussions regarding the financing of the pilot studies are ongoing.

In 2013, the Malaria Vaccine Technology Roadmap was updated to include licensure of vaccines targeting *Plasmodium falciparum* and *Plasmodium vivax* by 2030, with protective efficacy of at least 75% against clinical malaria, and that reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria infection¹⁹. The vaccine candidate pipeline is robust, and includes novel antigens and platforms⁴. Second generation vaccines are expected to provide higher protection than RTS,S in the longer term. Optimised tools are needed to measure incremental improvements and predict potential cost effectiveness of new candidates. The development of controlled human malaria infection (CHMI) models, efforts to harmonize elements of clinical trial design and standardization of various assays continue.

PDVAC stressed the importance of the development of 2nd generation malaria vaccines in parallel to the pilot implementation programme for RTS,S, and proposed that the current version of the vaccine roadmap be updated, potentially in 2018, in light of the RTS,S implementation.

1.4 Improved Influenza vaccines

In 2015, PDVAC noted that development of universal influenza vaccines will be challenging and protracted, particularly due to the lack of a regulatory pathway for novel antigens that operate through induction of T-cell immunity. Rather, PDVAC recommended that there be a focus on the definition of, and the collection of data to support implementation of 'improved' seasonal flu vaccines that would offer more immediate impact in LMICs. PDVAC advised WHO to develop strategic public health goals and PPCs for improved seasonal influenza vaccines, and to provide guidance on data requirements that would be needed to establish improved performance of such vaccines.

A working group has been established, and has proposed a draft statement of unmet public health need: 'Safe and well-tolerated influenza vaccines that are effective at preventing severe influenza illness, that provide protection beyond a single year, and that are programmatically suitable for use, are needed for low- and middle-income countries.' Two draft strategic goals have also been developed: the first is to promote incremental advancement in

influenza vaccine performance (in line with the 2015 PDVAC recommendations), and the second is to promote major advances toward a more universal-like influenza vaccine (in line with Global Vaccine Action Plan goals). These strategic goals, and the draft PPC for vaccines that induce broadly protective and long-lasting immune responses will be presented at the upcoming Eighth WHO meeting on development of influenza vaccines²⁰.

PDVAC reaffirmed the value of PPCs based on the two different approaches. There is a public health need to develop improved performance of currently available seasonal vaccines to offer protection over multiple seasons, and against drifted strains, with a view to generating shorter timelines to achieving availability and access in LMICs. As part of this effort, it will be necessary to define the criteria needed to demonstrate clinical benefit, and additional data requirements to support policy recommendations. Efforts to develop 'universal' vaccines that target conserved antigens, or conserved components of antigens, should continue in parallel, with a focus on identifying correlates of protection to support a regulatory pathway for this novel class of vaccines.

2. Enteric vaccine candidates

Diarrhea remains the second-highest killer of children due to infectious disease. Although mortality has declined over the past four decades, morbidity has not declined significantly, despite improvements in water and sanitation and benefits from oral rehydration therapy. There are nearly 2.7 billion cases of diarrheal disease every year, many with acute and chronic effects such as growth stunting and cognitive impairment. These long term sequelae significantly impact quality of life and economic potential, and are estimated to affect one-fifth of children globally. In 2015, PDVAC recommended that WHO expand its remit to include support for enteric vaccine development, particularly against Enterotoxigenic *Escherichia coli* (ETEC) and *Shigella*.

2.1 Enterotoxigenic *Escherichia coli* (ETEC) and *Shigella*

One of the main objectives of the planned WHO engagement in this area will be to ensure that the design of the phase III efficacy study, including definition of primary/secondary endpoints and long-term follow up, and the data generated, will be relevant to support a policy recommendation from SAGE. Activity is expected to begin in 4Q2016. Another key objective will be to develop a WHO Preferred Product Characteristics document which outlines WHO preferences, including considerations for development towards a potential combined vaccine.

Several vaccines are in development, with two ETEC candidates and seven *Shigella* candidates currently in clinical studies. For ETEC, the most advanced vaccine is ETVAX adjuvanted with dmLT, which is being developed for both a pediatric and traveller's indication. A phase I/II dose escalation, age de-escalation study in children is currently ongoing in Bangladesh, with intent to further age de-escalate into 6 week-old infants in late 2016. In parallel, a phase IIb study in travellers is planned to begin in 2017. Based on an encouraging phase IIb immunization and challenge study and additional positive protection studies in non-human primates (NHPs), an adhesin-based subunit ETEC vaccine (FTA) is moving forward with an accelerated clinical program designed to move a complete multi-valent vaccine into descending age field trials in 2020.

The most advanced *Shigella* candidate is Trivalent *Shigella* killed whole cell (TSWC) composed of formalin-inactivated *S. flexneri* 2a, *S. flexneri* 3a, and *S. sonnei*, expected to offer coverage across about 80% of isolates. A phase I study has been completed and a challenge trial with *S. flexneri* 2a prototype will begin in 4Q2016, followed by a study that will assess co-administration with ETVAX in 1Q2017. Both ETVAX and TSWC are being developed for oral administration.

Other promising *Shigella* vaccines in early stage clinical testing include two live attenuated vaccines, WRRS1 and ShigEETEC. WRRS1 is in a descending age study in Bangladesh, while ShigEETEC, which is a combination *Shigella*-ETEC combination vaccine, will begin a phase I study in early 2017. Three subunit approaches for *Shigella* are also in phase I/II studies; the prototype *S. flexneri* 2a bioconjugate vaccine (Flexyn2a), InvaPLex and the Generalized Module for Membrane Antigens (GMMA).

One of the critical strategic issues is whether to prioritize the licensure and approval of an ETEC vaccine, or to focus on the development of a combination with *Shigella* that will likely delay the timeline to vaccine availability. Epidemiologic data suggest that both intra- and inter-country disease heterogeneity is likely to exist and this may drive vaccine preferences, and presentation optimization. These data are critical to inform decision-making by country policymakers. For this reason, development of WHO derived preferred product characteristics for ETEC and *Shigella* vaccines, alone and in combination is needed.

2.2 Norovirus

In April 2016, PLOS released a collection on 'The Global Burden of Norovirus & Prospects for Vaccine Development'²¹, which includes the most current estimates on global Norovirus disease burden of over 200,000 deaths in low resource countries, and a global economic burden of more than \$60 billion²². Recent molecular analyses of samples from the community based longitudinal birth cohort MAL-ED study suggest that norovirus is the most common diarrheal pathogen in the first year of life, and the second most common in the second year of life.

There are 5 vaccine candidates in development, including three strategies to develop a combination vaccine against other enteric pathogens. However, only one candidate, which is composed of two VLPs based on the GI.I and GII.4 norovirus genotypes, has entered clinical studies, a Phase IIb study began recently²³. The advent of cell culture methods for norovirus will facilitate many advancements, including the optimization of a neutralization assay and enable the assessment of antisera against this vaccine to block binding of a diverse genotypes. In addition, in response to the 2015 PDVAC recommendation to consider incorporating norovirus surveillance within the WHO Global Rotavirus Surveillance Network, a survey of the capability and capacity at representative global sites has been performed to support a pilot study proposal.

The recently published epidemiology and burden of disease data indicate that norovirus fulfils the PDVAC criterion of unmet public health for a vaccine in LMICs. However, the ability of the candidates in the pipeline to offer protection over the range of circulating and emerging viral genotypes, and therefore the duration of protection of these vaccines, is currently unknown. It is conceivable that the vaccine will need to be periodically re-formulated, to include emerging genotypes. In addition to infants as a priority target population, adults and particularly the elderly are at risk, requiring the potential need for two vaccine formulations and/or presentations. Fortunately, at the current time, development of a norovirus vaccine that may offer efficacy in the context of low and middle income countries is proceeding with investment from the private sector, however an assessment of vaccine programmatic suitability and applicability to prequalification is needed, prior to Phase III trials to ensure the vaccine is appropriate for use in LMICs, assuming it is demonstrated to offer coverage over circulating genotypes within LMICs.

2.3 Second generation rotavirus

Rotavirus is the leading cause of severe diarrhea among all children below 5 years of age worldwide, causing 20-40% of severe diarrheal hospitalisations, and is associated with significant mortality, with the latest mortality estimates at 215,000 deaths in 2013²⁴. The introduction of the live-attenuated oral rotavirus vaccines, RotaTeq and Rotarix, in 2008 has had significant direct and indirect impact in countries where they are in use, including saving lives and reducing hospitalizations. However, in GAVI-eligible and LMIC countries in Asia and Africa the vaccine effectiveness is lower, with protective efficacy observed from 40-70% against severe rotavirusdiarrhea over the first year of life. Waning of protection has also been observed in these settings, with lower protection rates (25-50%) in the second year of life. In comparison, in high-income countries protection is higher (70-90%) and persists into the second year of life.

Thus, despite the enormous success of the live oral rotavirus vaccines, several challenges and issues remain such as the lower protection in GAVI-eligible and LMIC countries in Africa and Asia, together with the high cost of available vaccines. Despite an overall acceptable safety profile, the intussusception rate seems to be slightly increased by vaccination (occurrence 1 to 3 /100 000 oral Rotavirus vaccine recipients) in high income countries.

Several new oral, live-attenuated vaccines, composed of alternative strains, are in mid- to late-stage clinical development. The current WHO guidance document for the quality, safety and efficacy of oral live attenuated

rotavirus vaccines²⁵ would be applicable for these next generation oral, live-attenuated vaccines. Of these new oral rotavirus vaccines, Rotavac 20C (developed by BBIL) is the only vaccine currently licensed for use in children, having been approved for use in India in 2014. This vaccine is available on the private market in India and staged roll out in public health system is planned in four states in India. Another live rotavirus vaccine is being evaluated in a randomised placebo controlled trials in India (NCT02133690) and in Niger (NCT02145000).

Efforts are underway to develop non-replicating rotavirus vaccines (NRRV) as second generation rotavirus vaccines, which may avoid the risk of intussusception. The most advanced candidate is P2-VP8*, a trivalent truncated VP8* of rotavirus genotypes P[8], P[4] and P[6], currently in phase II clinical testing with a parenteral route of administration (NCT02646891).

For both NRRVs and additional oral, live-attenuated vaccines in development, PDVAC encouraged the rationalization of target product profiles for these new candidates, to clearly articulate the distinguishing/advantageous features over the existing vaccines, i.e. cost, safety, efficacy in LMIC, stability, breath of protection etc. The potential for any of these vaccine candidates to be included in combination with other emerging enteric vaccines will clearly be advantageous and should be encouraged and explorations of combination with IPV could be considered.

2.4 *Clostridium difficile*

Clostridium difficile is the leading cause of healthcare-associated diarrhoeal disease in the high-income countries, and is strongly associated with increasing age and frailty, immunodeficiency and in particular, modification of the normal flora through antibiotic use. The results of infection range from asymptomatic carriage through mild infection to severe diarrheal disease, with complications including pseudomembranous colitis and toxic megacolon. In the US alone, it is believed to have caused approximately 0.5 million infections and 29,000 deaths in 2012²⁶. Current interventions include antibiotic treatments, but their use can trigger relapse on withdrawal. Data on the burden of disease in LMICs is lacking, however hospital based studies in India, Thailand and South Korea suggest that the *C.difficile* infection is widespread, and global (Douce, manuscript in preparation).

There is a correlation between toxin neutralising antibody in human serum and disease protection; antibodies against toxin A are associated with protection against acute diarrhoea, whilst immune responses to toxin B appear to be effective against severe disease and relapse. Toxin-mediated disease is recapitulated in the Syrian Golden Hamster, which is the standard preclinical model for demonstration of proof of concept. Currently there are three vaccines in clinical development. A toxoid vaccine candidate (containing toxins A and B) recently completed a phase II study in healthy adults and demonstrated induction of high levels of neutralizing antibodies²⁷ and a phase III study has been initiated. A genetically modified, detoxified whole cell vaccine has also completed phase II, although results have not yet been reported. In phase I, the vaccine was shown to be safe and induced toxin-specific neutralizing antibodies that were sustained for 12 months²⁸. The third candidate is an adjuvanted recombinant protein encoding binding domains of both toxins, and the results of a phase I trial has been reported²⁹, and a phase II study has been completed. Passive immunity by administration of a monoclonal antibody is also in Phase III evaluation (NCT01513239 and NCT01241552).

PDVAC agreed that the role for WHO in facilitating *C.difficile* vaccine development is not clear given the lack of data regarding the disease burden in LMICs. However, it would be useful to understand the potential effectiveness of a vaccine in low resource contexts, and PDVAC raised the possibility of testing existing samples from the GEMS and MAL-ED studies for the presence of *C.difficile*. In addition, it would be helpful to assess the impact that these vaccines may have on reducing the use, and cost of antibiotics, and to consider this in the value proposition for vaccine decision-making.

2.5 *Helicobacter pylori* (*H.pylori*)

H.pylori is a highly motile, Gram-negative bacterium that infects the mucus layer lining the stomach. Infection typically occurs in childhood, although symptoms and clinical disease develop in only a minority of infected individuals during their lifetime. *H.pylori* is associated with gastritis, which causes several pathologies including gastric peptic and duodenal ulcer disease. Most significantly, long term infection can result in gastric

adenocarcinoma (GA) in later years of life; ~65-90% of GA cases are due to *H. pylori* infection. GA is the 3rd leading cause of death due to cancer, globally (~723,000 deaths in 2012, 8.8% of all cancers)³⁰. The global prevalence of *H. pylori* is believed to be approximately 50% with the highest mortality rates in East Asia and Eastern Europe.

The route of transmission is poorly characterised but the oral-oral route appears to be a common mechanism, as well as vertical transmission from mother to child. If untreated, most *H. pylori* infections are sustained for life, and ~15% of those infected are thought to develop an associated pathology. If diagnosed, *H. pylori* infections are currently treatable with combination antimicrobial therapies. However antibiotic resistance is increasing, with ~20% of patients in some countries currently failing first treatment and 5% failing two rounds of therapy. Antimicrobial treatment offers no protection against reinfection.

The choice of indication for an *H. pylori* vaccine is challenging: a prophylactic vaccine would likely need to be given to children in the first few years of life (to reach the maximum number of the target group while uninfected) but would need to offer long term protection to demonstrate clinical benefit against GA. An effective therapeutic vaccine however could be given at almost any age and would ideally be given by the 4th decade of life, prior to the peak of GA development which typically occurs from 50 years of age. The most advanced candidate is a urease toxin fusion approach and has completed phase III trials in children, in China, and demonstrated 71.8% efficacy against natural acquisition of infection³¹. However, next steps for this vaccine are not clear. Several other candidates are in preclinical development with one close to phase I studies.

PDVAC concluded that the burden of *H. pylori* is significant but that it will be logistically and technically challenging to demonstrate clinical benefit of a prophylactic vaccine given early in life, when there are rarely clinical symptoms of infection. Therapeutic candidates are currently too upstream in development for there to be a role for PDVAC.

3. Vaccines to be administered by maternal immunization

Maternal immunization is increasingly considered as a strategy to prevent maternal and/or neonatal disease. This approach has been proven to protect against maternal and neonatal tetanus and has been in place for decades. WHO recommends influenza and pertussis vaccination of pregnant women to prevent disease in mothers and newborns, respectively. However, for the first time there are now vaccines in development, specifically indicated for immunization of pregnant women as the target population. RSV vaccines are most advanced in this area followed by Group B Streptococcal vaccines.

Since the 2015 PDVAC meeting, a special journal issue dedicated to the issues regarding the maternal immunization vaccination strategy has been published and a great deal of work is underway to strengthen the maternal immunization platform³².

3.1 Respiratory Syncytial Virus (RSV)

Due to the advanced stage of RSV vaccine and monoclonal antibody development, RSV was presented to SAGE for information in April 2016. RSV causes 33.8 million episodes of lower respiratory infection (LRI) annually in children and approximately 200,000 deaths, 99% of which are in LMICs³³. Recently updated estimates for RSV acute and severe LRI (community based and hospitalized) disease and deaths will be published by the RSV Global Epidemiology Network (RSV-GEN) later this year. In addition, the pneumonia etiology research for child health (PERCH) study will present and publish results this year on the etiology of severe and very severe pneumonia in hospitalized infants and children in 9 sites in Africa and Asia. Preliminary data analyses indicate that RSV was the leading pathogen in infants with severe pneumonia in this study.

There are four RSV intervention strategies currently in development: 1) maternal immunization to enable passive transfer of maternal antibodies to the foetus *in utero*, 2) birth or early infant passive immunization with a long-acting monoclonal antibody, 3) active paediatric immunization and 4) vaccination of the elderly. The most advanced maternal immunization candidate begun phase III efficacy testing in late 2015 following the demonstration of induction of palivizumab competing antibodies (measured by ELISA) in women of childbearing age (PMID: 26259809)

and pregnant women. This efficacy trial has a group sequential design and will enroll 5,000 – 8,255 participants in a randomised placebo controlled trial across multiple sites in both the Northern and Southern hemispheres, and is expected to take 2-4 years to complete.

Monoclonal antibody development for the prevention of RSV in pediatrics is the next most advanced, with an extended half-life candidate (MEDI8897) that has been shown to be more potent in vitro than the currently licensed palivizumab. One dose may offer protection for up to 6 months. A phase IIb clinical study in infants born at 29-35 week gestation is planned, and the FDA recently granted fast-track designation for this product. Since the palivizumab patent recently expired, WHO in collaboration with the University of Utrecht will develop a 'biosimilar' of palivizumab and reduce costs for LMIC markets through high yield production and a novel financing plan³⁴. The estimated price is \$US 250 per child for the full 5 month dose series and the first market authorization is expected in late 2017.

Pediatric RSV vaccine candidates are the least advanced, however two adenovirus-based approaches have entered the clinic since the last PDVAC meeting. A chimp adenovirus (ChAd) candidate is currently in phase I testing in adults, to be followed by age de-escalation into seropositive, and ultimately seronegative infants. Ad26 and Ad35 are also being evaluated as a heterologous prime-boost regimen, currently in phase I testing in adults. A number of pediatric vaccine candidates developed by the Laboratory of Infectious Diseases, NIH are in phase I trials in infants and children. Of note, a vaccine containing a deletion of the M2-2 gene showed evidence of diminished replication, enhanced immunogenicity, and asymptomatic 'boosting' (anamnestic response) following naturally acquired RSV infection (PMID: 26537255).

Two vaccine candidates are in clinical development for the elderly with a post-fusion based adjuvanted nanoparticle in phase III efficacy testing, with data expected in late 2016/early 2017.

PDVAC fully supported the following SAGE recommendations and called for WHO and partners to develop plans to support global policy-making for RSV maternal immunization as well as passive immunization with long-acting mAb, following licensure. Particular areas of emphasis include: 1) RSV surveillance to determine seasonality and age-stratified RSV disease burden and community morbidity and mortality, especially in Africa and south-east Asia 2) assessment of the long term effects of RSV interventions and the potential impact of vaccination on reducing recurrent wheeze, which, if demonstrated, would substantially increase the cost-effectiveness and impact of RSV preventive interventions 3) generation of cost-effectiveness and impact data. SAGE also emphasized the need for strengthening of the maternal immunization platform in collaboration with the influenza, tetanus and pertussis vaccine communities, along with preparations for potential country introductions of RSV vaccine.

There is an urgent need to establish a WHO prequalification pathway for monoclonal antibodies, which does not currently exist. As a RSV vaccine or extended half-life monoclonal Ab may become available in the next 5 years, it will also be imperative to initiate early discussions with financing bodies, and to align with the GAVI Vaccine Investment Strategy (VIS) to avoid delay in achieving the potential major public health impact of RSV immunization if recommended for use by WHO.

3.2 *Group B Streptococcus (GBS)*

Globally, (GBS) remains the leading cause of sepsis and meningitis in young infants, with its greatest burden in the first 90 days of life. Intrapartum antibiotic prophylaxis (IAP) for women at risk of transmitting GBS to their newborns has been effective in reducing the young infant GBS disease burden in many high income countries, but IAP uptake is limited and difficult to implement in LMICs. Immunization of pregnant women with a GBS vaccine represents an alternative pathway to protecting newborns and young infants from GBS disease, through transplacental antibody transfer to the fetus in utero.

PDVAC prioritized GBS in 2015 and encouraged WHO to engage on developing guidance on the development pathway for GBS vaccines, including development of a PPC guidance document and a vaccine roadmap. In April 2016, WHO convened its first consultation on GBS vaccine development³⁵. The focus was on GBS maternal

immunization development programs targeting LMIC with the ultimate goal of reducing global newborn and young infant deaths. The major knowledge gaps about the disease burden characterization were identified. Recent data suggesting that GBS is an under-reported cause of stillbirth may have profound implications on the estimate of the global public health impact of a future GBS vaccine. The relationship between GBS colonization and prematurity should also be clarified. Disease surveillance in HIC also suggest an important residual unmet medical need, despite implementation of IAP.

Two major pharmaceutical companies are currently developing a multivalent polysaccharide conjugate vaccine, based on the available evidence of an association between trans-placental maternal-foetal transfer of antibodies targeting polysaccharides of the GBS envelope, acquired as a consequence of natural exposure, and a reduced risk of invasive infant disease. A vaccine incorporating five of the eleven described GBS serotypes is predicted to cover over 95% of the global circulating serotypes, but the risk of serotype replacement is unknown. An alternative approach is targeting surface expressed proteins, in an attempt to confer broad protection across all serotypes.

Epidemiological studies evaluating the role of maternal antibodies acquired following natural exposure will determine whether a protective threshold at birth can serve as an acceptable vaccine-induced correlate of protection. Until additional epidemiological and immunological data are available, estimating vaccine efficacy against invasive GBS disease in neonates and young infants in a double blind placebo-controlled vaccine trial remains the gold standard for generating the evidence required to determine potential public health impact and inform policy decision-making.

PDVAC endorsed the consensus-based prioritisation of future activities including the development of a PPC and vaccine development technology roadmap. Efforts should be made to raise awareness of the burden of GBS disease and potential public health value of a GBS vaccine, particularly in countries that lack local epidemiological data. As with RSV, efforts must be made to leverage and strengthen the maternal immunization platform by alignment with other vaccines that are administered in pregnancy, including the Brighton Collaboration's considerations for safety monitoring through the Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA)³⁶.

4. Vaccines that may reduce Antimicrobial drug resistance (AMR)

Antimicrobial-resistant infections currently claim at least 50,000 lives each year across Europe and the US alone, but AMR affects many hundreds of thousands in other areas of the world². In 15 European countries, more than 10% of bloodstream *Staphylococcus aureus* infections are caused by methicillin-resistant strains (MRSA), with several of these countries seeing resistance rates closer to 50%. Emerging resistance to treatments for other diseases, such as TB, malaria and HIV, have enormous impacts in lower-income settings, and by 2050, the death toll due to AMR infections in Africa is predicted to be approx. 4,000,000 per year. As mentioned above, each year almost 0.5 million cases of drug-resistant TB are reported, and these are extremely costly to treat; an MDR case costs 8-15 fold more to treat than drug a sensitive case, while an XDR case is 25-32 fold more expensive³⁷. The WHO estimates that approximately \$8 billion per year is required to support TB care and control efforts in LMICs. This is significantly more than the current investment in TB vaccine development programs.

At the Sixty-eighth World Health Assembly in May 2015, a global action plan to tackle antimicrobial resistance, including antibiotic resistance, was adopted³⁸. Its goal is to ensure continuity of successful treatment and prevention of infectious diseases with effective and safe medicines – including vaccines - that are quality-assured, used in a responsible way, and accessible to all who need them. The recommendations include increasing the use of existing vaccines, developing vaccines against high burden diseases currently treated systematically with antibiotics and prioritizing the development of vaccines for diseases where resistance is becoming a problem. Emerging AMR reduces the available treatment options for many pathogens in addition to those mentioned below, many of which are mentioned elsewhere in this report.

4.1 Group A *Streptococcus* (GAS)

GAS is a ubiquitous human pathogen that causes a broad disease spectrum, from mild to severe, the most serious of which is rheumatic heart disease (RHD). RHD affects approximately 30 million people globally, of whom 1 million experience heart failure and an estimated 300,000 die. GAS is also a major cause of invasive disease, with a case

fatality rate of 10-15% in high income countries, and as high as 38% in LMICs³⁹. On the milder end of the spectrum, GAS causes approx. 615 million cases of pharyngitis per year, resulting in 60-70% of cases being treated with broad spectrum antibiotics, rather than penicillin (9% of cases), to which GAS is universally susceptible. This extensive use of unnecessary and inappropriate antibiotics increases the likelihood of AMR emergence against antibiotics that are used to treat a range of pathogens.

Previous human challenge studies, as well as preclinical animal models suggest that it is feasible to develop a vaccine against GAS, and since the previous PDVAC meeting, phase I studies for one candidate has been initiated in adults, and two additional candidates are expected to enter phase I studies in the next 12 months. Despite this encouraging progress, significant debate remains as to the appropriate indication and optimal clinical endpoints, and the regulatory pathway for a vaccine to prevent or reduce RHD is unclear. In addition, there is a perception that increased prescription of penicillin would be an equally as effective and a significantly more cost effective method of reducing conditions that result from GAS infection. These issues are likely major stumbling blocks in incentivising investment in GAS vaccine development.

GAS has been prioritized by PDVAC previously, with a recommendation to develop a business case for both a global market, and also specifically for LMICs which would focus on prevention of severe outcomes in resource poor settings. Despite significant effort, it has been very difficult to engage stakeholders in this activity. PDVAC recommends that WHO convenes a consultation to examine the value proposition for GAS vaccines, considering its potential impact across both high income and lower income settings – including the consideration of how current treatment regimens may increase AMR, as well as to investigate the perceived regulatory obstacles.

4.2 *Staphylococcus aureus* (*S. aureus*)

S. aureus is a bacterium that is found as both an asymptomatic colonizer of the skin and nares of human hosts, as well as a frequent cause of human disease. It causes a spectrum of clinical manifestations of varying severity, and is the most commonly isolated pathogen from skin and soft-tissue infections, septic arthritis, pneumonia, endovascular infections, osteomyelitis, catheter/ other foreign-body infections, septicaemia, and toxic shock syndrome. Methicillin-resistant *S. aureus* (MRSA) has been documented to be emerging at a rapid and increasing rate since the antibiotic was first introduced in 1959, and hospital-associated MRSA (HA-MRSA) clones are now recognized to be the leading cause of nosocomial infections both in the United States and around the world, in high income as well as LMICs. The emergence of community-associated MRSA (CA-MRSA) in the past several decades is of concern, as is the emergence of highly resistant vancomycin-resistant *S. aureus* (VRSA).

To date, active and passive immunization approaches have been based on increasing the concentration of opsonic antibodies to single surface antigens, and all have failed to demonstrate protection. Antigenic variation, the multiple invasion pathways and lack of a surrogate of protection all present significant obstacles to vaccine development. Following the failure of single antigen vaccine approaches, most development efforts are now focused on multiple antigens, and a number of candidates are in preclinical development. One multi antigen approach, comprised of 4 antigens including two capsule polysaccharides (clumping factor A and a manganese transport) is the most advanced⁴⁰. Current efforts are also focused on further characterizing the immunopathology and immunity of *S. aureus* infections to identify new antigenic targets, and developing more representative preclinical models in which opsonising and/or neutralising immune responses are measured.

To date none of the vaccine candidates in development have contemplated target populations or indications that are prevalent in LMICs. Focus has been on development of a vaccine that will protect against life-threatening *S. aureus* infections in high income countries, but it is hoped that such a vaccine would also protect against all *S. aureus* infections including more commonly encountered skin and soft tissue infections, and therefore be applicable in LMIC contexts.

5. Sexually transmitted infections (STIs)

Since the 2015 PDVAC meeting, a new Global Health Sector Strategy on Sexually Transmitted Infections has been developed for 2016–2021 and adopted by WHO member states at the 69th World Health Assembly. Within this strategic framework, STI vaccine development was highlighted as key need for future STI control⁴¹. In addition, the

global roadmap for vaccines against STIs has been updated and included in the WHO Special Issue on pipeline vaccines published in *Vaccine*⁴². Currently, the only STI vaccine candidates that are undergoing or approaching clinical development are against herpes simplex virus (HSV) and *Chlamydia trachomatis*, and as such discussion was limited to these pathogens.

5.1 Herpes Simplex Virus

HSV is the leading cause of genital ulcer disease, and a particular concern for LMICs as it increases both acquisition and transmission of HIV infection. HSV type 2 and type 1 disease burden estimates were recently updated^{43,44}, and it is estimated more than half a billion people live with genital HSV infection, worldwide. PDVAC previously recommended that improved global estimates of neonatal herpes burden be generated, and assessment of available data has recently been completed with preliminary estimates of >14,000 new cases globally, an incidence rate of approx. 10/100,000 births, which is concerning because of a case fatality rate of 60% (Looker, submitted). The incidence is likely to be under-estimated in LMICs where HSV infection rates are highest and poor healthcare infrastructure means that neonatal herpes cases are likely to be undetected, but primary data are lacking. Ongoing evaluation of HSV infection as part of the Child Health and Mortality Prevention Surveillance (CHAMPS) network will help to address this burden gap.

At the 2015 meeting, the advance of therapeutic vaccine candidates for HSV-2 was highlighted, and the role of these types of vaccines in modulating the interaction between HSV and HIV acquisition was discussed as an important consideration for these vaccines in LMICs. In consideration of this, and with WHO support, a systematic review/meta-analysis of HSV-2 and risk of HIV acquisition including 54 studies will inform modelling of the potential impact of an HSV-2 vaccine on HIV incidence, and is expected to be published in late 2016. A review of biological mechanisms of HSV-HIV interaction and implications for vaccine development has also been drafted. The pipeline for therapeutic vaccines remains robust, with 5 candidates in clinical development, the most advanced of which now has data demonstrating significant reductions in HSV2 shedding (55%) and days with genital lesions (60%) over 12 months⁴⁵. In response to these positive data, NIAID has formed an HSV working group to propose desired characteristics for therapeutic and prophylactic vaccines for HSV, including indication, priority target populations, clinical trial endpoints, and safety and efficacy criteria. This document could form the foundation for a WHO consultative process to generate a guidance document on Preferred Product Characteristics (PPC).

PDVAC encouraged WHO to actively collaborate and support development of PPCs for HSV vaccines. The PDVAC committee itself will potentially expand to include an additional subject matter expert in the STI arena to help guide development of vaccines against these pathogens.

5.2 Chlamydia

Chlamydia trachomatis is a Gram-negative bacterium that can infect genital, ocular and lung epithelium. It includes three sets of serovars:

- Serovars Ab, B, Ba, or C — cause ocular trachoma, which can lead to blindness
- Serovars D-K — cause sexually transmitted infection resulting in urethritis, cervicitis, pelvic inflammatory disease (PID) (and associated infertility, ectopic pregnancy, and chronic pelvic pain), neonatal pneumonia, and neonatal conjunctivitis
- Serovars L1, L2 and L3 — cause lymphogranuloma venereum

C. trachomatis can ascend to the upper genital tract and cause pelvic inflammatory disease (PID), which can in turn lead to long-term sequelae including tubal factor infertility, ectopic pregnancy, and chronic pelvic pain. Other adverse outcomes of chlamydia include preterm birth, neonatal conjunctivitis and pneumonia, and increased HIV risk. Currently management is through screening programmes in some high income countries that are not feasible in resource constrained settings, where most cases are likely never diagnosed. WHO estimates that there were 131 million new cases of chlamydia in 2012⁴⁶ with most cases among adolescents and young adults. The global burden of chlamydia-associated PID, infertility and other sequelae has not been well characterized and estimates of the proportion of infertility presumed to be associated with genital infection (e.g., have a Fallopian tube etiology) in Africa are outdated⁴⁷, but are thought to be approx. 65-85% in women seeking fertility care.

There are several of vaccine candidates currently in preclinical development, with a subunit vaccine based on the chlamydial major outer membrane protein (MOMP) and live-attenuated (plasmid-deficient) approaches being the most advanced. Phase I trials are due to commence in 2016 and 2017, respectively. The intended goal of a chlamydia vaccine is to decrease upper genital tract sequelae, however PID is challenging to use as clinical endpoint as it is difficult to definitively diagnose and the causes of PID are multi-factorial (typically the result of *C. trachomatis* in 1/3 of cases). The chlamydia vaccine community is seeking guidance and consensus building on clinical endpoints for clinical studies, including evaluating the potential role of biomarkers, radiologic, and other measures of upper tract ascension, infection, inflammation and damage. Improved global burden of disease data and vaccine impact modelling on long term sequelae are also needed to define the investment case for these vaccines. PDVAC commended the progress towards the first vaccine study against chlamydia since the 1960s and look forward to discussing the path ahead once the early clinical data are available.

6. Currently under-utilised licensed vaccines

This section refers to vaccines that have been licensed, or are approaching licensure in some areas of the world, but are currently limited in their use outside any single WHO region. In some instances, the vaccines may have the potential of offering broader public health impact by expanding approval and use in other geographical regions, and PDVAC is seeking to understand the perspective in this regard.

6.1 Enterovirus 71 (EV71)

EV71 is one of the most common causes of hand-foot-and-mouth disease (HFMD). Sporadic EV71 outbreaks have occurred globally since it was first isolated in 1969, but from the late 1990s a series of large HFMD epidemics caused by EV71 have been reported in the Asia-Pacific region. In China alone, 7.2 million cases were reported between 2008 and 2012, of which 2,457 (0.03%) were fatal⁴⁸. Children less than 5 years of age have the highest risk of disease, and although infection is unusually mild and self-limiting, severe infections can result in neurological and cardiopulmonary complications, and death.

Several EV71 vaccine candidates are in development, and it was stated at the meeting that the Chinese national regulatory authority has licensed three EV71 vaccines. One of these is Sinovac's formalin-inactivated EV71 vaccine that has been approved for use on a 2-dose schedule, one month apart, to prevent EV71 disease in 6-71 month olds based on a Phase III study that demonstrated 95% efficacy over 12 mo⁴⁹. The Chinese Academy of Medical Sciences and Beijing Vigoo have also licensed inactivated EV71 vaccines in China (NCT01508247). All three vaccines are adjuvanted with aluminum hydroxide.

Given that EV71 outbreaks occur in other areas of the world (recently reported in Spain⁵⁰), further discussions are warranted in the international health community about how to assess the role of the Chinese vaccines during outbreaks outside China.

7. Emerging pathogens and the WHO R&D Blueprint

In the wake of the 2014-15 Ebola outbreak, various strategies were proposed to avoid such crises from reoccurring. Key to improving R&D preparedness and response is determining which pathogens are likely to be the greatest threat, creating consensus with respect to product development strategies and co-ordinating global funding for complementary R&D efforts going forward. To tackle these questions, and at the request of its 194 Member States, WHO convened a broad global coalition to develop the R&D Blueprint⁵¹ as a sustainable platform for accelerated R&D, with two complementary objectives:

- to develop (and implement) a roadmap for R&D preparedness for known priority pathogens, and
- to enable roll-out of an emergency R&D response as early and as efficiently as possible

The main approaches underpinning the improvement of preparedness within the R&D Blueprint include:

1. Assessing epidemic threats & defining priority pathogens
2. Developing R&D roadmaps to accelerate evaluation of diagnostics, therapeutics & vaccines
3. Outlining appropriate regulatory & ethical pathways

WHO has defined its priority list of pathogens within the published Blueprint. PDVAC has a contributory role within this framework, and when WHO declares a Public Health Emergency of International Concern (PHEIC), PDVAC may be tasked with forming a working group to facilitate development of guidance tools for the vaccine development community in the context of the emergency. For example, the current status of Ebola virus vaccine and Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV) vaccine development was reviewed by PDVAC at this and previous meetings, and a PDVAC Working Group is developing a WHO Zika vaccine Target Product Profile.

7.1 MERS-CoV

As reported in the 2015 meeting summary, a consultation to initiate work towards a MERS CoV roadmap was held in December 2015 with aims of defining the key basic and applied research activities, identifying the priority technologies and capacities to support vaccine development, and finally understanding the financing/procurement opportunities. Following this meeting, a draft roadmap was developed and underwent public consultation prior to finalisation and publication⁵².

7.2 Ebola virus

It is well accepted that the extraordinary rate of Ebola virus vaccine development was as a result of unprecedented collaboration and co-ordination of global vaccine R&D activities, and the availability of a number of candidate vaccines that could enter clinical phase evaluation⁵³. In the face of another PHEIC so soon following Ebola virus disease (EVD) outbreak, the global vaccine community is rallying, and reflecting on lessons learned from the experience in West Africa only 2 years ago. At the time of responding to the EVD emergency, the availability of well-characterised pre-clinical models and robust data was essential for the comparative evaluation and selection of candidates to move into clinical studies. Novel recombinant viral vector platforms, in combination with recombination proteins have been validated by EVD experience and it could be argued are now less risky for development of vaccine against future pathogens, but manufacturing feasibility and scale-up capabilities still need to be confirmed for the most novel platforms. Critically, sustainable public sector push and pull investment mechanisms beyond the initial emergency response phase need to be created, to incentivise manufacturers to engage in the long term commitment to developing and licensing vaccines that may only be used in outbreak or emergency scenarios.

PDVAC noted that there is now a call to develop a target product profile for a second generation Ebola virus vaccine that will likely cover several valencies, and will need to demonstrate longer duration of protection. WHO is developing a second generation EVD vaccine TPP to provide guidance about WHO's preferences and minimally acceptable criteria for vaccines in this area. During the discussion it was clarified that WHO TPPs include minimally acceptable criteria, whereas Preferred Product Characteristics specify only preferences.

7.3 Zika virus (ZIKV)

The status of Zika virus epidemiology, and the understanding of its pathogenesis and associated sequelae is evolving so rapidly that publications on these issues are almost immediately out of date. In preparation for PDVAC, a landscape analyses on ZIKV vaccine development status and prospects was revised (Barrett, in press, 2016). PDVAC's role has been to oversee a working group that has developed a target product profile (TPP) for use *in an emergency*, or future outbreak scenario. The TPP was made available for public consultation from 4th-23rd May, after which subject matter experts, global regulators, developers and manufacturers were convened to discuss the regulatory considerations for developing a vaccine with the characteristics described in the TPP. The finalised TPP and position paper arising from the meeting are in preparation and will be made publically available⁵⁴.

8. Cross-cutting product development and implementation issues

In addition to reviewing the status of vaccine development against pathogens, PDVAC considered a number of cross-cutting issues that could better integrate and therefore facilitate product development efforts for vaccines and other interventions.

8.1 Novel vaccine delivery technologies

In addition to the significant morbidity and mortality that drives the development of vaccines against pathogens for which vaccines are currently not available, the WHO estimates that there are approximately 1.5 million deaths per year in children under 5 from vaccine preventable diseases^{55,56}. One of the reasons for this striking immunization gap

is the cost and logistical challenges of delivery of these vaccines, over and above the cost of their manufacture. The remit of WHO's Immunization Practices Advisory Committee (IPAC) is to provide strategic advice on immunization practices, tools, and technologies intended to improve the delivery of immunization programmes at the country level. It oversees the recently formed delivery technologies working group (DTWG) composed of public health organizations, funders and procurement agencies as well as vaccine developers to evaluate R&D in novel delivery technologies and devices, for example the microarray patch, and compact, pre-filled auto-disable injection technologies (cPAD). Of particular focus for this group is the development and evaluation of a framework to analyze high-level trade-offs between important variables such as development, procurement and supply chain costs, coverage, efficacy, and safety in order to facilitate investment decisions by product developers, vaccine manufacturers, global policy makers, in-country decision makers and procurement agencies. This framework is referred to as total systems effectiveness (TSE). The intent of this delivery technology working group is to offer a platform for discussion and guidance regarding vaccine preferences for LMICs, early on in development, so that ultimately the vaccine is suitable for programmatic use. The DTWG reports directly to IPAC, but has potential overlap with activities that are overseen by PDVAC, particularly in consideration of second generation vaccines or new vaccines that may be developed with an alternative presentation to that of a needle and syringe.

PDVAC was supportive of the DTWG and encouraged continued communication between vaccine development and device/delivery technology development to identify potential opportunities novel combination product development.

8.2 The need for a WHO monoclonal antibody (MAb) prequalification pathway

There are several pathogen areas where MAb are being developed as vaccine-like interventions, as their single dose regimen and long half-life renders them amenable for LMICs contexts, where they could offer significant public health benefit. Candidates for RSV and rabies are approaching licensure within the next 5 years, and a WHO procedure for WHO prequalification is urgently needed to avoid delay implementation. This gap has been recognized and will be addressed.

8.3 PDVAC's role in and coordination with other vaccine/intervention development efforts

The scope of PDVAC overlaps with several other research agendas such as GVAP, AMR and, development and consolidation of maternal immunization platforms. The PDVAC research agenda needs to be clearly communicated, and PDVAC and IVB will strive to be well-informed of efforts in other research areas, to help shape and align strategy where appropriate. Future PDVAC meetings will consider these potential overlaps in more detail, as well as how PDVAC and IVB can facilitate development of integrated product development approaches.

9. PDVAC going forward

With the publication of vaccine pipeline analyses for 25 pathogens, and the discussion of seven new pathogens in 2016, PDVAC has effectively reviewed the landscape of emerging vaccines for the next 3 years. With RSV, TB, HIV and enteric candidates approaching pivotal data points, WHO will need to shift some focus to preparing for beyond licensure, and understanding what data are needed to support policy outcomes. Consultation with policy groups and procurement agencies will be key, as well as understanding the potential impact of vaccines within the broader control strategy – including diagnostics and other preventatives - for these pathogens. Vaccine impact modelling, and understanding the composite set of cost drivers through to vaccine delivery will be important. Interaction with WHO's IPAC and PQ teams will increase going forward, to strengthen the link between product development and programmatic requirements.

Under the recommendation of PDVAC, WHO will seek to broaden its role to support development of value propositions for vaccines against pathogens for which there is a poorly defined business case, for example GAS and HSV. Raising awareness of LMIC disease burden and requirements/procedures for access to LMICs markets may help to incentivise financing development of these vaccines. Of key consideration may be the potential for these vaccines to reduce the emergence of AMR, and PDVAC recommended that this be considered as a criterion in future landscape analyses and PPC guidance documents.

PDVAC and WHO will continue to align activities with the priorities within the WHO R&D Blueprint. PDVAC is aware that several other organizations which are responsible for emergency preparedness have been through a process to prioritize their R&D agendas, with some commonality and some complementarity to the pathogens listed in the WHO Blueprint. In this arena, PDVAC will continue its horizon scanning role, and will advocate for commitment to product development of vaccines for emerging diseases to progress through robust preclinical proof of concept to generation of phase I data, as a minimum. PDVAC strongly recommends the collaboration with other groups to coordinate advocacy and funding for vaccine development to prepare for the inevitable future emergencies.

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<http://www.who.int/wer>

Contents

- 389 Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC): summary of conclusions and recommendations, 30 May – 1 June 2016 meeting

Sommaire

- 389 Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC): résumé des conclusions et recommandations, réunion du 30 mai au 1 juin 2016

Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC): summary of conclusions and recommendations, 30 May – 1 June 2016 meeting

THEME: Research to minimize barriers and improve coverage of vaccines currently in use

Session 1: Missed opportunities for vaccination (MOV)

Introduction

As a follow-up to the IVIR-AC recommendations in 2014¹ the Committee considered a new methodology to assess missed opportunities for vaccination (MOV) as part of scaling-up the WHO MOV strategy. In order to assess the magnitude and causes of missed opportunities, the new methodology captures additional quantitative information, including explanatory demographic variables in combination with qualitative information based on anthropological variables. This is expected to yield more appropriate, better tailored interventions to reduce MOV within each local context.

Recommendations

- IVIR-AC supported the approach and commended the effort to incorporate qualitative assessment into the MOV strategy. Opportunities to assess MOV as a complement to assessing coverage in other facility-based surveys should be considered, such as in-depth assessments of data quality undertaken every 5 years. IVIR-AC also proposed exploring possibilities to analyse MOV in recent demographic and health surveys and the datasets of middle-income countries, and to conduct MOV surveys in some countries.

Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC): résumé des conclusions et recommandations, réunion du 30 mai au 1 juin 2016

THÈME: recherche pour réduire le plus possible les obstacles et améliorer la couverture des vaccins actuellement utilisés

Session 1: Occasions manquées en matière de vaccination

Introduction

Suite aux recommandations formulées par le Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC) en 2014,¹ le Comité a envisagé une nouvelle méthode d'évaluation des occasions manquées de vaccination dans le cadre des efforts entrepris par l'OMS pour intensifier la stratégie de réduction des occasions manquées. Pour évaluer l'étendue et les causes des occasions manquées de vaccination, cette nouvelle méthode intègre des informations quantitatives supplémentaires, notamment des variables démographiques explicatives, en combinaison avec des informations qualitatives fondées sur des variables anthropologiques. Cette approche devrait conduire à des interventions de réduction des occasions manquées mieux adaptées au contexte local.

Recommandations

- Le Comité a soutenu cette démarche et salué les efforts déployés pour inclure une évaluation qualitative dans la stratégie de réduction des occasions manquées de vaccination. Il a également suggéré qu'une analyse des occasions manquées pourrait être envisagée en complément de l'évaluation de la couverture dans le cadre d'autres enquêtes menées dans les établissements de santé, notamment l'examen approfondi de la qualité des données qui est réalisé tous les 5 ans. Le Comité a en outre proposé d'explorer la possibilité d'analyser les occasions manquées de vaccination à partir des enquêtes démographiques et sanitaires et des bases de données des pays à revenu intermédiaire, ainsi que d'effectuer des enquêtes sur les occasions manquées de vaccination dans certains pays.

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¹ See No. 1/2, 2015, pp. 1–8.

¹ Voir N° 1/2, 2015, pp. 1–8.

- The MOV survey is a recognized means of initiating a process to improve the issues of many health systems. The priority of locally-generated data should help to distinguish what is local and can be generalized, thereby facilitating effective communication and empowerment at all levels.
- IVIR-AC proposed standardizing and simplifying the language of the knowledge, attitude and practice (KAP) questionnaire and assisting with guidance on methodological issues such as the number of focus group discussions and key informant interviews to be conducted, and sampling strategies for both public and private sectors.
- The approach should include assessing the impact of MOV interventions. Longitudinal and follow-up surveys, and analysis of existing data, would be applicable – for example the use of district monthly coverage reports submitted to the WHO African Region.
- As implementation of the MOV assessment strategy and follow-up activities proceed, IVIR-AC recommends compiling a database of evidence for interventions and their impact on reducing MOV, thereby determining which are most effective.

Session 2: Non-specific effects (NSEs) of vaccines

Introduction

The IVIR-AC meeting in 2015 emphasized the importance of randomized trials within nested immunological studies. The Committee considered priority questions for NSE clinical trials, including trial designs for each priority question, as proposed by the participants of an ad-hoc consultation in February 2016.

Recommendations

- IVIR-AC considered the conclusion of the IVIR-AC meetings in 2014 and 2015² that further observational studies are unlikely to inform public health decision-making, thus reaffirming the importance of randomized clinical trials. The Committee acknowledged the progress made towards the refinement of priority research questions and trial designs resulting from the ad-hoc expert consultation, and also recommended that any trial design proposed should have its own rationale.
- IVIR-AC endorsed the designing of one or more protocols to assess the prospective non-specific effects of immunization on mortality. The work of the WHO Secretariat needs to be completed in preparing the protocols for the questions identified and trials outlined during the ad-hoc expert consultation of February 2016. These generic protocols would enable harmonized implementation of the trials across multiple settings. While further development of all the proposed trial designs is important, IVIR-AC recognizes that full evaluation necessitates a complete protocol. IVIR-AC will help inform decisions on feasibility and the selection of designs, and formulate questions.

² See http://www.who.int/immunization/research/committees/ivir_ac/en/index4.html

- Il est reconnu que les enquêtes sur les occasions manquées permettent d'engager un processus d'amélioration de nombreux aspects des systèmes de santé. Le fait d'accorder la priorité aux données générées localement devrait faciliter la distinction entre ce qui relève du niveau local et ce qui est généralisable, favorisant ainsi une autonomisation et une communication efficace à tous les niveaux.
- Le Comité a proposé d'harmoniser et de simplifier certains libellés du questionnaire Connaissances, attitudes et pratiques (CAP) et de fournir des orientations d'ordre méthodologique, par exemple sur le nombre de discussions en groupes thématiques et d'entretiens d'informateurs clés à mener, ainsi que sur les stratégies d'échantillonnage, tant dans le secteur privé que public.
- Il convient que cette approche comprenne une évaluation de l'impact des interventions de réduction des occasions manquées. Cette évaluation peut se fonder sur des enquêtes longitudinales et de suivi, ainsi que sur l'analyse de données existantes, par exemple en s'appuyant sur les rapports mensuels de couverture soumis par les districts au Bureau régional OMS de l'Afrique.
- Durant la mise en œuvre et le suivi de la stratégie d'évaluation des occasions manquées, le Comité recommande de constituer une base de données regroupant les informations sur les interventions menées et sur l'impact observé en termes de réduction des occasions manquées, ce qui permettra d'identifier les interventions les plus efficaces.

Session 2: Effets non spécifiques des vaccins

Introduction

En 2015, le Comité avait souligné l'importance de la réalisation d'essais cliniques randomisés intégrant des études immunologiques. Le Comité a examiné des questions prioritaires concernant les essais cliniques sur les effets non spécifiques des vaccins, portant notamment sur la méthodologie d'essai pour chacune des questions prioritaires proposées par les participants d'une consultation spéciale tenue en février 2016.

Recommandations

- Le Comité a rappelé les conclusions auxquelles il était préalablement lors de ses réunions de 2014 et de 2015 du Comité², selon lesquelles les études d'observation ne suffisent probablement pas à fournir des données à l'appui du processus décisionnaire en matière de santé publique, réaffirmant ainsi l'importance des essais randomisés. Le Comité s'est félicité des progrès tangibles accomplis pour affiner les questions prioritaires de recherche et la conception des essais en s'appuyant sur une consultation spéciale d'experts; il a également recommandé de veiller à ce que toute méthodologie d'essai proposée ait son propre fondement logique.
- Le Comité a approuvé l'élaboration d'un ou plusieurs protocoles d'évaluation prospective des effets bénéfiques et préjudiciables non spécifiques de la vaccination sur la mortalité. Le travail entrepris à cet égard par le Secrétariat de l'OMS devra être mené à bien par la préparation de protocoles pour les questions identifiées et les essais évoqués lors de la consultation spéciale d'experts de février 2016. Ces protocoles génériques permettront une mise en œuvre harmonisée des essais dans divers contextes. Bien qu'il soit important de poursuivre le développement de toutes les méthodes d'essai proposées, le Comité reconnaît qu'une évaluation complète exige un protocole pleinement abouti. Le Comité guidera la sélection des méthodes d'essai sur la base de leur faisabilité et contribuera à la formulation des questions.

² Voir http://www.who.int/immunization/research/committees/ivir_ac/en/index4.html

- IVIR-AC members will continue to guide future WHO consultations, and review and comment on the protocols while being developed.

THEME: Research to conduct impact evaluation of vaccines in use

Session 3: WHO vaccine-preventable disease (VPD) evidence synthesis tool

Introduction

In 2014, IVIR-AC recommended that WHO facilitate a “hub” of work to assess the burden of disease and its economic impact, to include an associated network of experts. The WHO Secretariat commissioned the work through a competitive bidding process and presented the Committee with a preliminary draft which included the underlying tools used to synthesize the evidence.

Recommendations

- The VPD evidence synthesis tool should contain evidence vetted by WHO for decision-making criteria or parameters and should create and support discussion during country-level decision-making processes.
- The tool should be linked to the National Immunization Technical Advisory Committee (NITAG) Resource Center and other sites including the National Institute for Health Research SYSVAC,³ a database of systematic research on vaccines and immunization.⁴
- WHO should establish standard operating procedures to define how the emerging content will be vetted and updated to the portal (including timelines).
- Special attention should continue to be given so that common challenges of sustainability and comprehensiveness of the tool are anticipated and addressed.
- Main targets of the portal should be policy-makers and supporting staff, particularly those of NITAG including its secretariats and decision-makers.
- Follow-up meetings should be arranged to discuss and plan data visualization and communication efforts.

Session 4: Rotavirus mortality

Introduction

Rotavirus is a recognized cause of mortality from diarrhoea in children; however there is considerable disagreement on the number of deaths that occur each year. IVIR-AC was presented with a comparison of 3 sources of estimates (global, regional and national) of deaths from rotavirus in children aged <5 years⁵ for the year 2013 that aimed to identify the drivers of such difference.

Recommendations

- State directly that most deaths from diarrhoea reflect a lack of access to health care to provide

- Durant l'élaboration des protocoles, les membres du Comité continueront de fournir des avis et commentaires dans le cadre de futures consultations auprès de l'OMS.

THÈME: recherche pour évaluer l'impact des vaccins utilisés

Session 3: Outil OMS de synthèse des données sur les maladies à prévention vaccinale

Introduction

En 2014, le Comité avait recommandé que l'OMS œuvre à l'établissement d'une plateforme de travail, comportant un réseau associé d'experts, pour évaluer la charge et l'impact des maladies. Le Secrétariat OMS a émis un appel d'offres pour faire exécuter ce travail et a soumis au Comité un avant-projet de la plateforme, ainsi que les outils associés de synthèse des données.

Recommendations

- L'outil de synthèse des données sur les maladies à prévention vaccinale contient des données vérifiées par l'OMS pour les critères/paramètres de prise de décision et il devrait permettre de susciter les débats et de soutenir le processus de prise de décision au niveau national.
- Il convient de relier cet outil aux centres d'appui pour les groupes consultatifs techniques nationaux sur la vaccination (NITAG) et à d'autres sites, notamment à la base de données SYSVAC du National Institute for Health Research,³ constituée d'études systématiques sur les vaccins et la vaccination.⁴
- Il convient que l'OMS établisse des modes opératoires normalisés pour définir la manière dont les nouveaux contenus seront vérifiés et mis à jour dans le portail (et selon quel calendrier).
- Une attention particulière devrait continuer à être portée à la nécessité d'anticiper et de résoudre les problèmes courants de pérennité et d'exhaustivité de l'outil.
- Le portail devrait principalement être destiné aux responsables politiques et au personnel d'appui, en particulier les secrétariats et les décideurs des NITAG.
- Des réunions de suivi devraient être prévues pour examiner et planifier les efforts de communication et de visualisation des données.

Session 4: Mortalité due aux rotavirus

Introduction

L'infection à rotavirus est une cause reconnue de mortalité diarrhéique chez l'enfant. Toutefois, les estimations du nombre de décès provoqués chaque année par les rotavirus divergent sensiblement. Le Comité a pris connaissance d'une étude comparative des estimations provenant de 3 sources différentes (mondiale, régionale et nationale) de la mortalité liée aux rotavirus chez les enfants de <5 ans⁵ pour l'année 2013, l'objectif étant d'identifier les facteurs responsables de la divergence des estimations.

Recommendations

- Indiquer clairement que la majorité des décès liés à la diarrhée relèvent d'un manque d'accès aux soins de santé à des fins de

³ SYSVAC is a database of systematic reviews on vaccines and immunization.

⁴ See <http://immunisation.hpru.nihr.ac.uk/sysvac>

⁵ Child Health Epidemiology Reference Group (CHERG), Institute for Health Metrics and Evaluation and WHO/Centers for Disease Control.

³ SYSVAC est une base de données d'études systématiques sur les vaccins et la vaccination.

⁴ Voir <http://immunisation.hpru.nihr.ac.uk/sysvac>

⁵ Groupe de référence pour l'épidémiologie de la santé de l'enfant (CHERG), Institute for Health Metrics and Evaluation et OMS/Centers for Disease Control.

rehydration which results from dysfunctional health-care systems. Assessment of basic health-care services should be incorporated into the presentation and analysis of mortality.

- Understand that estimates of mortality from rotavirus derive from the attribution of aetiology to total deaths from diarrhoea. Therefore, the same comparable sources for aetiology and mortality data should be used.
- Clarify that the purpose of this process is not to create one rotavirus mortality estimate, but to benefit from lessons learned from each estimate and to guide health decision-makers in their consideration of the sources and nuances of the data.
- Continue to improve data sources; consider how to address uncertainty of estimates; consider finer-grained strata (important for impact assessment of on-time or delayed vaccination); evaluate the impact of different covariates in the model; and compare the implications of national and subnational data.
- Reliance on proprietary data limits the capacity of interested parties to understand rotavirus mortality estimates, and to conduct independent analyses. IVIR-AC should therefore examine and address strategies for optimally sharing databases and issue a recommendation regarding this at a future meeting.

Session 5: Guide for disease and economic impact model comparisons

Introduction

As a follow-up to the IVIR-AC recommendation of 2015, the Committee emphasized the need for guidelines on the best practice for conducting disease and economic impact model comparison exercises. A preliminary framework of the model comparison was presented to the Committee for review.

Recommendations

- IVIR-AC considered that the framework proposed for model comparison was appropriate and that an IVIR-AC working group should be established to develop this.
- One of the goals of model comparison is to report and understand variability and uncertainty between models while taking into account parameter, structural and methodological uncertainty. In order to do this, model comparison exercises need to standardize reporting rather than modelling methods. To correspond with existing checklists, such as the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement, and to allow for results to be reproduced, modelling methods should be transparent.
- Reporting of a model quality assessment is encouraged.
- Pooling models through a weighting score should be considered in future model comparison studies.
- IVIR-AC noted that the informatics capacities now available for modellers and a wide array of scientists make the issue of how to approach transpar-

réhydratation, imputable au dysfonctionnement des systèmes de santé. Une évaluation des services de santé de base devrait être incluse dans la présentation et l'analyse de la mortalité.

- Reconnaître que les estimations de la mortalité liée aux rotavirus dépendent de l'attribution de l'étiologie à l'ensemble des décès d'origine diarrhéique. Il importe donc d'utiliser les mêmes sources comparables de données pour l'étiologie et la mortalité.
- Préciser que l'objectif de cette démarche n'est pas de générer une estimation unique de la mortalité due aux rotavirus, mais d'exploiter les enseignements tirés de chaque estimation afin de guider les responsables des décisions sanitaires en tenant dûment compte des sources et des nuances des données.
- Le Comité recommande de continuer d'améliorer les sources de données; de réfléchir à la manière d'aborder l'incertitude des estimations; d'envisager l'étude de tranches d'âge plus étroites (ce qui est important pour évaluer l'impact de la vaccination, selon qu'elle est réalisée conformément au calendrier ou avec retard); d'évaluer l'effet de diverses covariables du modèle; et de comparer les implications des données nationales et infranationales.
- L'utilisation de données de propriété exclusive restreint la capacité des parties intéressées à interpréter les estimations de la mortalité liée aux rotavirus et à mener des analyses indépendantes. Il est donc souhaitable que le Comité examine et élabore des stratégies permettant un partage optimal des bases de données et émette une recommandation à ce sujet lors d'une prochaine réunion.

Session 5: Guide pour la comparaison des modèles sur l'incidence économique et l'impact sur les maladies

Introduction

Suite à la recommandation qu'il avait formulée en 2015, le Comité a souligné la nécessité d'élaborer des lignes directrices sur les meilleures pratiques pour la réalisation d'études de comparaison des modèles sur l'incidence économique et l'impact sur les maladies. Un cadre préliminaire de comparaison des modèles a été soumis au Comité pour examen.

Recommandations

- Le Comité a estimé que le cadre proposé pour la comparaison des modèles était satisfaisant et qu'un groupe de travail du Comité devrait être constitué pour faire progresser cette initiative.
- L'un des objectifs de la comparaison des modèles est d'exposer et de comprendre la variabilité et l'incertitude existant entre les modèles en tenant compte de l'incertitude des paramètres, de l'incertitude structurelle et de l'incertitude méthodologique. Pour ce faire, les exercices de comparaison des modèles doivent se concentrer sur la standardisation du mode de présentation des résultats plutôt que sur celle des méthodes de modélisation. Conformément aux listes de contrôle existantes, comme celles des lignes directrices GATHER (Guidelines for Accurate and Transparent Health Estimates Reporting), et afin d'assurer la reproductibilité des résultats, les groupes de modélisation doivent présenter les méthodes utilisées de manière transparente.
- Il est conseillé de procéder à une évaluation de la qualité des modèles et d'en communiquer les résultats.
- Dans les futures études de comparaison, on pourra envisager une mise en commun des modèles avec un coefficient de pondération.
- Le Comité a observé qu'au vu des capacités informatiques dont disposent aujourd'hui les spécialistes de la modélisation, ainsi qu'un large éventail de scientifiques, la question de la transpa-

ent, open databases particularly germane and important to facilitate model comparison exercises, and for advancing implementation research in general. Other groups such as Chatham House, and leading journals have been exploring this topic; IVIR-AC should obtain consensus opinions from other forums, and consider inviting appropriate participants who could provide relevant perspectives and input for discussions during a future meeting.

Session 6: Human papillomavirus (HPV) modelling in low- and middle-income countries

Introduction

As a follow-up to a WHO ad-hoc expert consultation in 2015 on priorities for HPV vaccine research in general disease and the economic impact, IVIR-AC proposed modelling activities specifically to compare 9-valent versus 2/4-valent vaccines; gender-neutral versus girls-only vaccination strategies; and 3-dose versus 2-dose schedules in low- and middle-income countries (LMICs). The modelling framework and plans to address the questions were presented to IVIR-AC for review.

Recommendations

- IVIR-AC endorsed the proposed framework to evaluate different HPV immunization strategies, particularly the intention to review systematically the burden of HPV-related cancers and anogenital warts, immunogenicity and efficacy of HPV vaccines in clinical trials, and effectiveness in post-introduction impact evaluations. Through modelling, the framework would also encourage the estimation of incremental effectiveness and cost-effectiveness of gender-neutral HPV immunization and catch-up vaccination compared with the currently recommended “girls-only” strategy.
- In the short term (within the second quarter of 2016), modelling with the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) tool should be conducted to contrast the cost-effectiveness of bivalent, quadrivalent and nonavalent vaccines in 179 countries of the strategy targeting girls only. The inclusion of population-level herd effects in PRIME is advised. With regards to the adaptation of transmission-dynamic models – which have been helpful to support policy-making in high-income countries – key issues relating to HPV immunization effectiveness in LMIC (such as variability of sexual behaviour, cervical cancer-screening patterns, and background HPV infection rates) should be characterized. Finally, the worldwide burden of anogenital warts, including by serotype, should be systematically reviewed to provide input data to further modelling.
- In the medium and long terms, transmission-dynamic models adapted to LMICs should examine the effectiveness and cost-effectiveness of different HPV immunization strategies comparing “no vaccination” and in combination with cervical cancer

rence et de l'accessibilité des bases de données revêt une pertinence et une importance particulières pour faciliter la comparaison des modèles et, de manière plus générale, faire progresser la recherche sur la mise en œuvre. D'autres groupes, tels Chatham House, ainsi que certaines revues scientifiques de renom ont déjà abordé ce sujet. Il conviendrait donc que le Comité recueille les opinions de consensus exprimées au sein d'autres forums et envisage d'inviter certaines personnes susceptibles d'apporter des éléments pertinents de réflexion et de discussion à participer à une prochaine réunion.

Session 6: Modèles relatifs au papillomavirus humain (PVH) dans les pays à revenu faible ou intermédiaire.

Introduction

Suite à la consultation spéciale d'experts organisée par l'OMS en 2015 pour examiner les priorités générales de recherche sur le vaccin contre le PVH, des activités de modélisation de l'incidence économique et de l'impact sur la maladie ont été proposées, visant spécifiquement à comparer: le vaccin nonavalent et les vaccins bivalent et quadrivalent; les stratégies de vaccination, selon qu'elles ciblent les 2 sexes indifféremment ou les filles uniquement; et les schémas d'administration à 3 ou 2 doses dans les pays à revenu faible ou intermédiaire. Le Comité a pris connaissance du cadre de modélisation et des modalités envisagées pour répondre à ces questions.

Recommandations

- Le Comité a approuvé le cadre proposé pour évaluer différentes stratégies de vaccination contre le PVH, en particulier, le fait de prévoir l'examen systématique de la charge des cancers et des condylomes ano-génitaux liés au PVH, de l'immunogénicité et de l'efficacité potentielle des vaccins anti-PVH dans les essais cliniques, ainsi que de leur efficacité réelle dans les études d'impact menées après l'introduction du vaccin. Il pourrait en outre favoriser, par modélisation, l'estimation de l'efficacité et du rapport coût/efficacité supplémentaires que représenteraient la vaccination des 2 sexes et la vaccination de rattrapage contre le PVH par rapport à la stratégie recommandée actuellement, qui ne cible “que les filles”.
- À court terme (cours du deuxième trimestre 2016), il convient de procéder à une modélisation à l'aide de l'outil PRIME (Papillomavirus Rapid Interface for Modelling and Economics) pour comparer le rapport coût/efficacité des vaccins bivalent, quadrivalent et nonavalent dans 179 pays, dans le cadre de la stratégie visant uniquement les filles. Il est recommandé d'inclure les effets de l'immunité collective au niveau de la population dans la modélisation PRIME. En vue d'une adaptation des modèles dynamiques de transmission – qui se sont avérés utiles pour appuyer l'élaboration des politiques dans les pays à revenu élevé –, il importe de caractériser certains paramètres clés liés à l'efficacité de la vaccination anti-PVH dans les pays à revenu faible ou intermédiaire (par exemple variabilité des comportements sexuels, tendances en matière de dépistage du cancer du col de l'utérus et taux de base d'infection par le PVH). Enfin, la charge mondiale des condylomes ano-génitaux devrait être examinée de manière systématique, y compris en fonction du sérotype, pour générer des données à inclure dans de nouvelles modélisations.
- À moyen et long terme, on utilisera les modèles dynamiques de transmission adaptés aux pays à revenu faible ou intermédiaire pour étudier l'efficacité et le rapport coût/efficacité de différentes stratégies de vaccination contre le PVH, en comparant les scénarios « sans vaccination » à ceux où la vaccination est associée à

screening strategies, schedules and vaccine types. This work may start by re-calibrating the existing individual-based HPV model to the specific situation of 3–6 LMICs. Given the complexity of transmission-dynamic models, IVIR-AC suggests the use of one or more emulators that serve as user interfaces to simplify the evaluation of a variety of permutations, thereby facilitating in-country assessments and local ownership of effectiveness and cost-effectiveness analyses.

Session 7: Influenza-specific economic guidelines

Introduction

IVIR-AC reviewed the WHO influenza disease and economic value chain – a set of guidance documents and tools that supports country-level decision-makers in assessing the economic and social benefits of introducing influenza vaccination or expanding existing vaccination to specific target groups, such as pregnant women, health workers and older people.

Recommendations

- IVIR-AC suggested that the WHO influenza disease and economic value chain should include epidemiological surveillance standards; that the underlying data should include local information from a variety of sources; and that the value chain should address how to communicate the evidence and results from economic studies with decision-makers.
- WHO should support the sharing of existing country experience regarding consideration of disease and economic burden in policy- and decision-making in order to generate policy demand for such studies in other settings.
- The original question to IVIR-AC on the use of a fixed cost-effectiveness threshold is beyond the scope of this Committee due to it being related to general cost-effectiveness in health rather than specifically to vaccines. However, if countries have not gone through the process of defining their cost-effectiveness thresholds, IVIR-AC recommends they use alternatives such as 1) benchmarking against the least cost-effective health interventions already funded by relevant jurisdictions; 2) using cost-effectiveness league table approaches; and/or 3) transferring outcomes (in either DALY⁶ or QALY⁷ format) into monetary units for benefit to cost ratios or return on investments.
- Economic burden outcomes should clarify who bears the costs of the disease in question.
- IVIR-AC recommends that the influenza vaccine-specific economic evaluation guidelines should recognize differences in the effectiveness and cost-effectiveness of various influenza vaccines based on presentation, formulation, and circulating types and subtypes that vary over time and place.

des stratégies de dépistage du cancer du col de l'utérus ou est effectuée avec différents calendriers et différents types de vaccin. La première étape de ce travail pourra consister à adapter le modèle individuel existant pour le PVH à la situation particulière de 3 à 6 pays à revenu faible ou intermédiaire. Compte tenu de la complexité des modèles dynamiques de transmission, le Comité propose d'employer un ou plusieurs émulateurs servant d'interfaces avec l'utilisateur afin de simplifier l'évaluation de diverses permutations, facilitant ainsi la réalisation des évaluations dans le pays et favorisant l'appropriation locale des analyses de l'efficacité et du rapport coût/efficacité.

Session 7: Orientations économiques pour la grippe

Introduction

Le Comité a examiné la chaîne de valeur économique et sanitaire de l'OMS pour la grippe. Il s'agit d'un ensemble de documents d'orientation et d'outils destinés à aider les décideurs au niveau national à évaluer les avantages économiques et sociaux d'une introduction du vaccin contre la grippe ou d'une extension de la vaccination antigrippale à certains groupes cibles particuliers, comme les femmes enceintes, les agents de santé ou les personnes plus âgées.

Recommandations

- Le Comité a proposé que la chaîne de valeur économique et sanitaire de l'OMS pour la grippe contienne des normes relatives à la surveillance épidémiologique; que les données associées comprennent des informations locales provenant de sources diverses; et que la chaîne de valeur aborde les modalités de communication des données et des résultats d'études économiques aux décideurs politiques.
- L'OMS est invitée à soutenir l'échange des expériences acquises par les pays sur la prise en compte de la charge sanitaire et économique de la maladie dans le processus de décision et l'établissement des politiques afin de générer une demande politique pour ce type d'étude dans d'autres contextes.
- La question initialement adressée au Comité quant à l'utilisation d'un seuil fixe applicable au rapport coût/efficacité n'est pas du ressort du Comité car il ne s'agit pas d'une question propre au vaccin, mais plutôt d'une question plus générale de rentabilité dans le domaine de la santé. Toutefois, le Comité recommande aux pays n'ayant pas encore procédé à la définition de leur seuil coût/efficacité d'adopter une variable différente, notamment: 1) en établissant une comparaison avec les interventions sanitaires présentant le plus faible rapport coût/efficacité déjà financées par les autorités compétentes, 2) en utilisant un tableau de classement du rapport coût/efficacité, et/ou 3) en transformant les résultats (exprimés en DALY⁶ ou en QALY⁷) en unités monétaires pour obtenir un rapport coût/bénéfice ou un retour sur investissement.
- Les résultats relatifs à la charge économique devront préciser quels segments de la société supportent les coûts en question.
- Le Comité recommande que les lignes directrices relatives à l'évaluation économique du vaccin contre la grippe tiennent compte des différences d'efficacité et de rapport coût/efficacité entre les différents vaccins antigrippaux, selon leur présentation, leur formulation et les types et sous-types en circulation, qui varient en fonction du temps et de l'emplacement géographique.

⁶ DALY: disability-adjusted life year.

⁷ QALY: quality-adjusted life year.

⁶ DALY: années de vie ajustées sur l'incapacité.

⁷ QALY: années de vie ajustées sur la qualité de vie.

Session 8: Cholera disease burden

Introduction

IVIR-AC reviewed an effort to map estimates of reported subdistrict cholera incidence with the prospect of inferring the global burden of cholera including extrapolation to areas with little or no data available.

Recommendations

- The investigators should acknowledge more clearly that their model is descriptive rather than predictive. A predictive model for cholera is unlikely to be accurate in view of limited data and the diversity of transmission patterns and risk factors, which change over time and in various geographical settings. In addition, arbitrarily small geographical units, and the paucity of high-quality data on detection and incidence, limit the accuracy of predictive models for cholera.
- The model structure should start with questions posed (for example on the purpose of developing the model and graphs); confirmation of the target audience and how the model would be of benefit; confirmation of its potential use for advocacy, for immunization recommendations by NITAG secretariats, by the GAVI Alliance, for public health messaging or for impact assessment.
- The modelling effort at global level should focus on issues identified by the Global Taskforce for Cholera Control and the GAVI Alliance being key decision-makers on the use of vaccines.
- Data sources should be clearly identified, including the number of cases, the time period of acquisition, geography, source, and whether cases are suspected or confirmed.
- Outbreaks of cholera (e.g. variation from baseline) should be distinguished from endemic disease. Maps should include both since public health implications and interventions differ based on whether cholera is changing from baseline or is static.
- The model should distinguish confirmed cases from suspected cases, to determine whether, and to what extent, epidemiological patterns change, if at all.
- Uncertainty needs to be better acknowledged with regard to knowledge of the disease, the unpredictable spread of cholera due to the diversity of transmission patterns, and risk factors.

THEME: Research to improve methods for monitoring of immunization programmes

Session 9: Immunization E-Registries (IERs)

Introduction

Electronic immunization registries (IERs) facilitate coverage monitoring in terms of particularity, timeliness and accuracy. The Committee reviewed a conceptual framework to identify research barriers

Session 8: Charge de morbidité du choléra

Introduction

Le Comité a examiné les efforts entrepris pour établir une carte des estimations de l'incidence du choléra signalée dans les sous-districts afin d'en déduire la charge mondiale de la maladie, y compris par extrapolation dans les zones où les données sont rares ou inexistantes.

Recommandations

- Les chercheurs devraient reconnaître plus clairement que leur modèle est descriptif, et non prédictif. Les modèles prédictifs du choléra ont peu de chances d'être exacts, compte tenu de la quantité limitée de données disponibles et de la diversité des modes de transmission et des facteurs de risque, qui évoluent dans le temps et varient selon l'emplacement géographique. En outre, l'utilisation d'unités géographiques arbitrairement petites et le manque de données de haute qualité sur l'incidence et la détection des cas compromettent l'exactitude des modèles prédictifs sur le choléra.
- La structure du modèle doit commencer par les questions soulevées, c'est-à-dire la finalité des efforts de modélisation et des graphiques. Elle doit confirmer l'audience cible et l'utilité que revêt le modèle pour cette dernière, en indiquant notamment s'il est destiné au plaidoyer, à la formulation de recommandations par les secrétariats des NITAG, à un usage par l'Alliance GAVI, à la communication de messages sur la santé publique ou à une étude d'impact.
- Les efforts de modélisation devraient être axés au niveau mondial sur les questions identifiées par le Groupe spécial mondial de lutte contre le choléra et l'Alliance GAVI, des organes qui jouent un rôle déterminant dans la prise de décisions sur l'utilisation des vaccins.
- Il importe d'identifier clairement les sources des données, notamment en ce qui concerne le nombre de cas, la période d'acquisition, l'emplacement géographique, la source et le statut suspect ou confirmé des cas.
- Il convient de faire la distinction entre les flambées (variation par rapport à la situation de référence) et le choléra endémique et de veiller à ce que les 2 figurent sur les cartes, car les conséquences en termes de santé publique et les interventions à mener diffèrent selon que la maladie présente un écart par rapport à la référence ou demeure relativement stable.
- Il importe que les cas confirmés et les cas suspects soient abordés de manière distincte dans le modèle pour identifier toute évolution éventuelle du tableau épidémiologique et déterminer l'ampleur de cette évolution.
- Il importe de mieux reconnaître l'incertitude existante, liée aux connaissances sur la maladie et au caractère imprévisible de la propagation du choléra, imputable à la diversité des modes de transmission et des facteurs de risque.

THÈME: recherche pour améliorer les méthodes pour le suivi des programmes de vaccination

Session 9: Registres électroniques de vaccination

Introduction

L'utilisation de registres électroniques de vaccination peut faciliter le suivi de la couverture vaccinale, rendant ce processus plus spécifique, plus rapide et plus exact. Un cadre conceptuel visant à identifier les obstacles à la recherche sur la mise en œuvre de registres

to implement IERs for monitoring immunization programmes.

Recommendations

- IVIR-AC appreciated the value of work presented and acknowledged its potential use within countries for supply chain evaluations, pharmacovigilance, vaccine coverage and effectiveness studies.
- IERs can be regarded as a tool for implementation research, for example by indicating the immunization status of hard-to-access populations and by linking IER with civil and birth registrations.
- The work on IERs should be linked to a similar study at PATH,⁸ funded by the Bill & Melinda Gates Foundation to identify barriers for implementing IERs in the United Republic of Tanzania and Zambia.
- The work on IERs should focus on country-level programme managers since some might be opposed to moving from paper to e-registries, particularly if both are used in a transition period.
- Paper registries have a long history of use in measuring immunization coverage and individual immunization status; countries choosing to implement IERs should ensure, demonstrate and disseminate that, in comparison with existing methods and relative to cost, IERs improve efficiency in terms of data accuracy, effectiveness and timeliness.
- IVIR-AC suggests WHO support the development of IERs in various ways such as by identifying circumstances in which they can be successfully introduced; identifying the “killer risks” to avoid failures; and identifying resources needed to ensure their long-term sustainability.
- IVIR-AC recommends that research and implementation of IERs should be prioritized and that WHO should find ways of making financial and human resources available. ■

⁸ PATH: Program for Appropriate Technology in Health.

électroniques pour le suivi des programmes de vaccination a été examiné par le Comité.

Recommandations

- Le Comité a accueilli favorablement le travail accompli, estimant qu'il pourrait faciliter les études sur la chaîne d'approvisionnement, la pharmacovigilance, la couverture vaccinale et l'efficacité des vaccins dans les pays.
- Les registres électroniques de vaccination peuvent servir d'outil de recherche sur la mise en œuvre, permettant notamment de déterminer le statut vaccinal des populations difficiles d'accès en reliant les registres électroniques de vaccination avec les registres des naissances et de l'état civil.
- Un lien devrait être établi entre ce travail et une étude semblable menée par PATH⁸ et financée par la Fondation Bill & Melinda Gates, qui vise à identifier les obstacles à la mise en œuvre de registres électroniques de vaccination en République-Unie de Tanzanie et en Zambie.
- Les travaux menés sur les registres électroniques de vaccination devraient principalement s'adresser aux administrateurs des programmes au niveau des pays, certains d'entre eux étant susceptibles de s'opposer au passage des registres papier aux registres électroniques, en particulier s'ils utilisent les 2 en période de transition.
- Les registres papier sont utilisés de longue date pour mesurer la couverture vaccinale, ainsi que le statut vaccinal individuel; les pays qui décident d'adopter les registres électroniques de vaccination devront vérifier, démontrer et communiquer le gain d'efficacité offert par cette approche par rapport aux méthodes existantes en termes d'exactitude des données, d'utilité et de délai au regard des coûts.
- Le Comité propose que l'OMS soutienne le développement des registres électroniques de diverses manières, en particulier en identifiant les circonstances qui se prêtent à une introduction réussie des registres électroniques, les «risques certains» d'échec et les ressources nécessaires pour garantir la pérennité à long terme des registres électroniques.
- Le Comité recommande que la priorité soit accordée à la recherche et à la mise en œuvre des registres de vaccination et que le Siège de l'OMS s'emploie à mettre à disposition des ressources financières et humaines à cet effet. ■

⁸ PATH: Program for Appropriate Technology in Health (Programme de technologie appropriée pour la santé).

How to obtain the WER through the Internet

- 1) WHO WWW server: Use WWW navigation software to connect to the WER pages at the following address: <http://www.who.int/wer/>
- 2) An e-mail subscription service exists, which provides by electronic mail the table of contents of the WER, together with other short epidemiological bulletins. To subscribe, send a message to listserv@who.int. The subject field should be left blank and the body of the message should contain only the line subscribe wer-reh. A request for confirmation will be sent in reply.

Comment accéder au REH sur Internet?

- 1) Par le serveur Web de l'OMS: A l'aide de votre logiciel de navigation WWW, connectez-vous à la page d'accueil du REH à l'adresse suivante: <http://www.who.int/wer/>
- 2) Il existe également un service d'abonnement permettant de recevoir chaque semaine par courrier électronique la table des matières du REH ainsi que d'autres bulletins épidémiologiques. Pour vous abonner, merci d'envoyer un message à listserv@who.int en laissant vide le champ du sujet. Le texte lui-même ne devra contenir que la phrase suivante: subscribe wer-reh.

22-23 August ' 2016

12th Meeting of the SAGE Polio Working Group

Conclusions and recommendations

Note for the Record



DRAFT AS OF 9/28/16

Background

The 12th face-to-face meeting of the SAGE Polio Working Group (WG) was held during 22-23 August 2016 at the World Health Organization in Geneva, Switzerland.

The meeting was attended by the following WG members: Yagob Al-Mazrou (Chair), Peter Figueroa (Ex-chair), Elizabeth Miller (Ex-chair), Walter Orenstein, Antoine Kabore, Kimberly Thompson, Nicholas Grassly, Walter Dowdle, Hyam Bashour and T Jacob John. Francis Nkrumah and Zulfiqar Bhutta were unable to attend.

This note presents a summary of the main findings, conclusions and recommendations of the meeting.

Context and objectives of the meeting

In April 2016, SAGE expressed its concern over the global supply shortage of Inactivated Poliovirus Vaccine (IPV), which will persist into 2017-18. SAGE urged that IPV suppliers make best efforts to fulfil their commitment to supply IPV, accommodate the needs of the programme (e.g. supplying more vaccine in 1-dose or 5-dose vials to reduce wastage), and inform the SAGE Polio WG of any further change in the IPV supply situation.

SAGE reviewed the Polio WG discussion on future polio immunization policy and requested the WG present a high-level policy direction in October 2016, and finalize its recommendations on future immunization policies for consideration by SAGE in October 2017.

The specific objectives of the WG meeting were:

1. To review the cVDPV2 epidemiology after the OPV2 withdrawal
2. To review the lessons learned from OPV2 withdrawal and discuss any follow-up issue (e.g. IPV shortage, catch-up vaccination, containment), including reassessment of type 2 response protocol
3. To discuss the risks associated with full OPV withdrawal and needs for bOPV campaigns prior to the switch
4. To discuss the roadmap for the SAGE discussions on future immunization policy (including duration of vaccination after OPV withdrawal, criteria to stop poliovirus vaccination and options for post-OPV immunization schedule)
5. iVDPV epidemiology and surveillance strategy

Topic 1: cVDPV epidemiology after the OPV2 withdrawal

The WG reviewed progress towards interruption of type 1 wild poliovirus (WPV1) and type 2 circulating Vaccine-Derived Poliovirus (cVDPV2).

WPV1

In the last six months, WPV type 1 cases have occurred in Nigeria, Pakistan and Afghanistan. As of 15 August 2015, the year to date case count in 2016 is 26 (41 in 2015). There are 14 cases in Pakistan (32 in 2015), 9 cases in Afghanistan (9 in 2015) and 3 cases in Nigeria (0 in 2015). 73 WPV1 positive samples were detected in Environmental Surveillance in both countries. In Afghanistan and Pakistan, there are two corridors of active transmission on both sides of the border (i.e. Nangarhar/Kunar-Khyber/Peshawar/Bannu and Kandahar-Helmand/Baluchistan). In Afghanistan and Pakistan, accessibility and Supplementary Immunization Activities (SIA) quality have continued to improve in 2016, but access remains an issue. The current challenges include: 1) critical gaps in SIA quality in Pakistan (especially in Karachi and northern Sindh as well as in high-risk mobile and underserved populations), and 2) the need to increase access in the Eastern region, and to improve SIA quality in accessible areas in Afghanistan.

In Nigeria, after the absence of WPV detection since 2014, two WPV1 cases were detected in Borno (Jere and Gwoza LGA) in July 2016. Accessibility in most of Borno State remains highly compromised due to ongoing conflict. Genetic sequencing results of samples collected from the cases, suggests that these two viruses are closely related but not identical; furthermore, that these viruses were circulating undetected since 2011, which

indicates ongoing programmatic failures to reach un- and under-vaccinated populations in these areas. The Global Polio Eradication Initiative (GPEI) plans to conduct a rapid outbreak response with 5 bOPV immunization rounds (the first was conducted during 15-22 August), targeting the immediate outbreak area as well as surrounding Lake Chad Basin countries. Until April 2016, a considerable proportion of Acute Flaccid Paralysis (AFP) cases occurring among children of internally displaced families in safe areas of Borno were incorrectly reported using their original home address in conflict-affected inaccessible parts of the state recorded as their residence, not the place of case detection, which occurred in accessible areas, giving the inaccurate view that surveillance was taking place in areas where there was actually no surveillance. This misallocation of addresses has been corrected.

Due to the outbreak response in Nigeria and other SIAs, the global supply of bOPV will be constrained. The programme is reviewing planned SIAs in other countries to manage bOPV supply. The WG also raised concerns about delaying preventive SIAs that the programme needs to conduct to maintain high population immunity.

cVDPV2

The WG reviewed cVDPV2 outbreak in Myanmar and Guinea, which were reported in the second half of 2015.

Myanmar has not detected any cVDPV2 case since 5 October 2015. The outbreak response assessment determined that “cVDPV2 transmission may have been interrupted”, however uncertainty remains due to gaps in surveillance.” The WG expressed concern that the outbreak response SIAs failed to achieve high coverage in insecure areas.

Guinea detected 7 cVDPV2 cases in 2015 and conducted 4 SIAs after the last case. While no cases have been detected in 2016, the outbreak response assessment determined that “circulation may not have been interrupted” and recommended intensifying surveillance as well as preparing for mOPV2 response if needed.

Since the switch from tOPV to bOPV in April 2016, there has been one continuing cVDPV2 outbreak since November 2014 (Nigeria, with 32 nt changes from Sabin 2 and 20 nt difference from the closest match), and six VDPV events (one AFP case in Nigeria with 8 nt changes, three ES detections in India with 8-14 nt changes and two ES detections in Pakistan with 8-12 nt changes). Nigeria conducted three mOPV2 campaigns as a response to the cVDPV2 outbreak. In addition, in Hyderabad, India, a fractional dose IPV (fIPV) outbreak response campaign was conducted to address immunity gaps, the first ever undertaken globally. The target group for the fIPV campaign were children aged from 6 weeks to 3 years (estimated to be 291,305 children). The campaign was limited to areas from which sewage drains to the Amberpet sewage treatment plant and which were considered at high risk of a potential outbreak of cVDPV, based on coverage of routine immunization and the quality of prior polio campaigns (such as in Hyderabad district); it was also conducted in the adjoining high-risk slum and migrant populations of Rangareddy district. Overall, the quality of ID injection, vaccine utilization per vial, and campaign coverage was high: 80-90% observed injections demonstrated bleb formation; 40-47 fractional doses utilized/10 dose vial, and an estimated >90% coverage was achieved.

Over the next 12 months, the priorities of the programme include: 1) Ensuring high quality coverage of outbreak response activities in Nigeria, and all 5 Lake Chad basin countries, 2) Continued support to Pakistan and Afghanistan (e.g. implementation of National Emergency Action Plan for Polio Eradication (NEAP), improvement of SIAs quality, additional allocation of IPV for 2017 SIAs), 3) Reassessing risk in all security compromised areas (e.g. Nigeria, Afghanistan, Pakistan but also Syria, Somalia, Sudan, Iraq, Yemen), 4) Maintaining political advocacy and resource mobilization, and 5) Strengthening and sustaining outbreak response capacity at global and regional levels.

The WG reviewed the status of detection of type 2 Sabin poliovirus through environmental and AFP surveillance, after the switch. Historically, in other countries (e.g. New Zealand, Yogyakarta in Indonesia, and Cuba), poliovirus was not detected from the environment 2-3 months after the switch from OPV to IPV. In Nigeria and Pakistan, type 2 poliovirus was not detected within six months after the last tOPV campaign was conducted (with continued tOPV in RI). After the type 2 withdrawal, Sabin type 2 was not detected through environmental surveillance in Afghanistan, Kenya, and Pakistan since July 2016. In Nigeria, Sabin type 2 was not detected through environmental surveillance, except for Borno, Jigawa, and Lagos, possibly due to mOPV2 campaigns being conducted in Borno. AFP surveillance did not detect Sabin 2, 3 months after the switch (August 2016), except in a few countries (Ethiopia, Nigeria, South Sudan and Somalia). The global experience

with OPV2 cessation also shows behaviour consistent with that predicted by modelling studies of OPV evolution and cessation, as summarized in the previous WG note.

The analysis of surveillance data also indicated the variance in performance in environmental sites (e.g. ability to detect Sabin virus after OPV campaigns). For example, in Nigeria, some environmental sites have less than 50% probability of detecting Sabin polio virus after an SIA. There are also significant variations in processing time (i.e. time between stool collection and entry in PolIS, and lab results). In most regions, it often took more than 40 days for data to be entered into PolIS and more than 100 days to obtain lab results.

WG decisions/recommendations

- The WG noted the significant progress in responding to and eliminating cVDPV2 after the switch, and highlighted that the disappearance of Sabin 2 poliovirus detected through environmental and AFP surveillance, is encouraging.
- The WG expressed concern over the unexpected detection and prolonged circulation of WPV in Nigeria, as well as continuing “persistent” cVDPV2 detection, and reiterated the importance of monitoring surveillance quality especially in access-limited areas (including the Lake Chad area).
- The WG recommended that the programme closely monitor and manage the supply/demand of bOPV, particularly as the outbreak response in Lake Chad will increase bOPV demand. The WG proposed not to exclude the use of tOPV in Nigeria to address WPV1 and cVDPV2 at the same time, if any manufacturers still have any tOPV available. It also urged the programme to maximize bOPV production to ensure sufficient supply, and that the programme increases its forecasts for vaccine needs.
- The WG recommended considering expansion of environmental sites and/or validating the sample analysis in high risk areas.

Topic 2: Implementation of OPV2 withdrawal

Lessons learned from OPV2 withdrawal

The WG received an update on OPV2 withdrawal. The switch was completed in all OPV using countries between 17 April and 1 May 2016. Indicators tracking the successful implementation of the switch were outlined and specific approaches to switch implementation were highlighted. Key strategies contributing to the success of the switch were emphasized, including strong partnership; clear distribution of roles; ownership at the country and regional level; defined timeframe; timely dissemination of guidance and updates; and dedicated funding and EPI staff support to facilitate country efforts. It was noted that a few countries (e.g. Iraq, Vietnam) as well as OPV suppliers, still hold tOPV stocks, therefore the program is closely following up with these countries and sites to ensure these stocks are destroyed.

IPV supply situation

The WG reviewed the current IPV supply situation. To date, 104/126 countries previously using tOPV-only have introduced one dose of IPV into their RI schedules. However, due to significant ongoing constraints in supply, 40% less IPV has been available than what was awarded through the initial UNICEF tender in 2014. As a result, 43 countries (about 22% of the global birth cohort) will face delays in IPV introduction or re-supply until Q4 of 2017. Specific mitigation measures to manage the IPV supply constraints were highlighted, including prioritizing supply to tier 1 and 2 countries (request for additional doses will be considered on a case by case basis); limiting supply to tier 3 and 4 countries; and the use of fIPV in outbreak response activities. The WG was in agreement regarding the need for catch-up vaccination for birth cohorts born after 1 May 2016 in countries where IPV introduction is delayed or disrupted.

Surveillance

The WG reviewed the quality of surveillance in high risk countries following OPV2 withdrawal (particularly countries with delayed IPV introduction or resupply, low OPV3 coverage, or history of cVDPV). Following the SAGE recommendation in April 2016, WHO amended the surveillance case definition to include type 2 Sabin so that all type 2 polioviruses will be notified under the International Health Regulations.

Surveillance indicators in most of the 36 tier 1 and 2 countries, either reach or surpass global standards at the national level, except for Azerbaijan, Equatorial Guinea, Indonesia, Philippines, Cambodia, Laos, Timor-Leste,

and Papua New Guinea. Sub-national surveillance gaps remain in all tier 1 and 2 countries; however, it was noted that recent improvements towards closing these gaps have taken place in a number of tier 1 and 2 countries (i.e. Mauritania, Mali, Guinea, Central African Republic, Democratic Republic of the Congo, Mozambique and Madagascar). In addition, 14 of 36 tier 1 and 2 countries are conducting environmental surveillance, and 4 countries in Africa plan to establish environmental surveillance soon.

Surveillance indicators in the majority of the 43 countries without IPV (due to delayed introduction or resupply) either reach or surpass standards at national level, with surveillance gaps remaining at the sub-national level. However, some countries continued to have problems to achieve standard quality indicator levels at the national level, including Ebola affected countries (Sierra Leone and Liberia), Morocco, Djibouti, Sri Lanka, and DPRK. WHO will work with the Ministries of Health (MoH) in these countries to assess the situation and implement surveillance strengthening measures. Environmental surveillance was established in 7 of 43 countries; with a plan to expand to 5 additional countries in Africa.

Given the recent detection of cVDPV2 and WPV1 in Nigeria despite national surveillance indicators reaching global standards, there is an evident need for continued close monitoring as well as undertaking gap analysis 'beyond the indicators', including analysis of the impact of security, conflict and migration and possibility of over-reporting non-AFP.

Containment

The WG reviewed the progress towards the implementation of GAP III requirements, particularly in the context of formal declaration of the eradication of WPV2 in 2015 and OPV2 withdrawal in April 2016. An overview of the two phases of GAP III were detailed: the objective of phase I to reduce the number of facilities designated to handle poliovirus serotype 2; the objective of phase II, to reduce the risk of release of poliovirus and reduce the consequences of release from the designated facilities. Currently the programme expects that 21 countries will host 58 designated poliovirus essential facilities (32 labs, 6 IPV producers, 20 Sabin IPV producers).

Since the last WG meeting in October 2015, there has been significant progress, particularly regarding: 1) communication to regions, countries and facilities; 2) targeted engagement with countries at risk of lagging behind; and 3) intensified efforts for GAP III implementation.

To accelerate the implementation of GAP III, WHO is establishing a Containment Advisory Group (CAG) to provide further technical guidance on the implementation of GAP III. WHO is strengthening its headquarters containment team, and has conducted 10 regional GAP III implementation and certification workshops. Phase I implementation is ongoing for WPV2 and cVDPV2 (phase Ia), and Member States were expected to report regarding OPV2/Sabin2 (phase Ib) by 31 July 2016, however, most countries have not completed phase to date. The WG encouraged the programme to recognize containment as an issue with the same or greater level of complexity as the coordination of the tOPV-bOPV switch, and urged the programme to significantly increase its staff and financial resources to manage containment.

Specific supporting activities to achieve implementation of GAP III were detailed, including the three phases of the Containment Certification Scheme; development of a pool of GAP III experts/auditors to provide technical support; the work in progress to align the WHO Technical Report Series 926 to GAP III; and development of guidance to classify Sabin samples into three risk categories (which is anticipated to be completed in September 2016). In terms of next steps, countries will nominate expert members to establish their National Authority for Containment (NAC), and the terms of reference and timelines for approval are being developed for selected members from the Global Certification Commission, who would provide oversight to the process.

Outbreak response protocol

The WG reviewed the results of a recent Bangladesh study (unpublished), which assessed seroconversion against poliovirus type 2 induced by one or two doses of mOPV2 administered in different immunization schedules and the role of IPV. In the study, subjects received first mOPV2 doses at 6 weeks, followed by the second doses given after 1-, 2- or 4 weeks. Other subjects received two mOPV2 doses at 6 and 10 weeks with IPV administered concurrently with the first mOPV2 dose. One dose of mOPV2 administered at 6 weeks induced immune response in 91% of subjects (after 4 weeks), with no difference between groups with IPV and groups without IPV. Two doses of mOPV2 administered at short intervals (1, 2 and 4 weeks) induced immune response in 93%, 95% and 97%, respectively, with the differences in immune response not being statistically significant.

The WG reviewed the possible implication of the results of this study, to the type 2 outbreak protocol. The WG agreed that coverage represented the key issue and suggested that high quality SIAs (i.e., >95% coverage in all areas, including the inaccessible ones) such that two mOPV2 doses are sufficient to protect individual children (without IPV). One workgroup member emphasized that population immunity to transmission is what needs to be managed, not individual immunity measured by the study, and the programme needs to consider both the individuals not reached by the outbreak response vaccine either directly or through secondary spread. In addition, no specific data assesses and compares the effect of mOPV2 alone versus mOPV+IPV on pre-existing mucosal immunity, although modelling studies suggest little benefit of the added IPV dose when giving both mOPV and IPV to the same vaccine recipient with respect to population immunity. In addition, the WG repeatedly emphasized the importance of ensuring high immunization coverage of outbreak response SIAs.

WG decisions/recommendations

- The WG commended the global and regional teams and countries for the successful implementation of tOPV-bOPV switch
- The WG expressed strong concern over the continued IPV supply shortage and encouraged WHO/UNICEF to continue to explore alternative options such as new IPV suppliers and adjuvanted IPV.
- The WG recommended catch-up vaccination of the missed children in countries with delayed IPV introduction when sufficient supplies of IPV become available. The WG requested WHO/UNICEF develop a priority algorithm for allocating additional IPV supply.
- The WG recommended that instead of focusing on the number of mOPV2 SIAs for outbreak response, the programme should focus on reaching all children with high coverage, which could imply fewer than the originally proposed rounds (i.e. minimum of 5 in zone 1 and 2, and 4 in zone 3 to 2-3, depending on the coverage achieved and transmission risk (zone)). In principle, mOPV2 is the primary choice of vaccine in outbreak areas. However, especially for OPV-primed populations, the addition of 1 fractional IPV dose may be considered in the outbreak affected area during SIA2 or SIA3 in combination with mOPV2, where operationally feasible, providing mOPV2 SIA coverage is not compromised. For response to an aVDPV, responding with one SIA using ID fractional IPV may be considered for highly OPV primed populations and otherwise low risk settings.
- The WG recommended increasing investment to facilitate GAP III implementation to accelerate the implementation of Phase I and II, as well as to ensure the provision of necessary technical support.

Topic 3: Risks associated with full OPV withdrawal

The WG reviewed analysis by two modelling groups (Kid Risk and Institute for Disease Modelling) on VDPV 1 and 3 emergence risks after the full OPV withdrawal and need for additional bOPV campaigns prior to the withdrawal.

Modelling groups agreed that the risk of cVDPV 1 and 3 emergence at the time of bOPV cessation should be relatively low in most countries, because the current population immunity against type 1 and 3 is high, due to the introduction and continued use of bOPV and IPV in routine immunization schedules. If the current level of routine bOPV and IPV coverage is maintained, most countries will not require additional bOPV campaigns prior to OPV cessation. However, if bOPV SIAs are not maintained and population immunity to transmission drops prior to OPV cessation, then areas with high force of infection and low RI coverage (especially in areas with under-vaccinated and/or inaccessible sub-populations), will need to conduct multiple bOPV campaigns prior to bOPV cessation to prevent cVDPVs after bOPV cessation.

WG decisions/recommendations

- The WG encouraged the programme to ensure high routine immunization (bOPV+IPV) coverage in areas with under-vaccinated/inaccessible populations.
- The WG suggested the programme consider maintaining ongoing preventive SIAs in countries with insufficient routine immunization coverage and additional bOPV campaigns prior to OPV cessation in countries (areas) where population immunity remains low. The WG also emphasized the importance of the programme continuing to target and reach un- and under-vaccinated populations (e.g. those in inaccessible areas) until successful OPV cessation.
- The WG emphasized the importance of securing sufficient supply of bOPV including a stockpile for outbreak response.

Topic 4: Future immunization policy

In April 2016, the Polio WG proposed that SAGE work on future immunization policy, including: (i) an explicit decision on whether polio vaccination should be continued after global certification of eradication; (ii) the recommended IPV schedule (number of doses, timing, and formulation) after OPV withdrawal; and (iii) the criteria for when countries could stop polio vaccination. The WG began its discussions of specific recommendations and identified data needs to support discussions at its next meeting.

Currently, the programme anticipates OPV withdrawal in 2020 or 2021, one year after Global Certification Commission (GCC) certification of WPV eradication (i.e. 4-5 years after the last WPV1 case and minimum one year between GCC certification to OPV withdrawal).

Regarding future immunization policy, countries fall into 3 broad categories: 1) Countries hosting poliovirus essential facilities whereby GAP III requirements necessitate ongoing and indefinite routine immunization with IPV (Sabin retaining countries should have at least one dose of IPV with coverage \geq equal to or greater than DTP3; WPV-retaining countries should have at least three IPV doses with $\geq 90\%$ coverage); 2) Countries maintaining IPV for country-specific reasons (e.g. national security and bioterrorism risk); and 3) "all other countries".

The WG discussed the requirements for IPV in "all other countries," and agreed that these countries should maintain IPV in the routine immunization for some time (e.g. 5 or 10 years) after OPV cessation to maintain high population immunity against possible VDPV emergence, iVDPV excretion, as well as containment failure. Modelling identified the greatest expected incremental net benefits for a strategy of all countries continuing at least one dose of IPV in routine immunization for 5 years after bOPV cessation. Further modelling studies would be needed to explore additional options raised by members of the WG

The WHO secretariat proposed that in the post-OPV era, all countries should aim to achieve $\geq 90\%$ population immunity against all three serotypes, to minimize the risks for poliovirus re-emergence from residual VDPV/WPV, containment failure, and iVDPV. The WG agreed this level of population immunity will require at least two fractional or two full IPV doses (for prime and boost). For example, studies have shown that either two full dose IPV doses (administered at 2 and 4 months) or two fIPV doses (administered at 4 and 8 months) could achieve 90% seroconversion against all serotypes.

The WG discussed the potential use of fractional dose IPV to effectively stretch limited supply. However, operational aspects of fractional dose in routine immunization (e.g. acceptability, wastage, operational feasibility, and cost) should be further analysed and clarified to inform SAGE in determining its position on fIPV doses in routine immunization.

For countries choosing to use hexavalent vaccine containing IPV, the schedule and number of doses will likely be determined based on other antigens.

The WG reviewed the projected estimates of global IPV demand and supply. The IPV market may become more competitive around 2020 due to the potential production scale-up of existing suppliers and the establishment of new mostly Sabin IPV suppliers. However, significant uncertainties remain regarding future IPV supply and the WG needs to consider IPV supply issues in the context of any future recommendations that it makes regarding immunization schedules. A 2 IPV dose schedule will require at least 80M additional doses (or more if some countries choose to use 3 or more doses of combination vaccine) which may not be available in 2020, depending on the speed at which number producers effectively come on the market

The WG invited two IPV suppliers (Sanofi and Bilthoven Biologicals) to discuss their production scale-up plan and perspectives on future immunization policy. Both suppliers indicated that they anticipate significantly increasing the supply to UNICEF market by 2018. Both manufacturers requested clarity on the future immunization policy (e.g. duration of IPV, number of IPV doses, availability of sustained funding) to make a timely decision on their supply and necessary investment. Suppliers also noted that attention to GAP III implementation roadmaps is critical to support continuing IPV availability. The WG noted that in the absence of a GPEI strategic plan extending beyond 2018, financial commitments to all programmatic efforts remain

uncertain and recommended that the programme should initiate efforts to develop a strategic plan that will extend further in time.

WG decisions/recommendations

- The WG emphasized the importance of advance preparations/communications for OPV withdrawal to facilitate OPV withdrawal following GCC certification of WPV eradication.
- The WG recommended countries without polio essential facilities should maintain IPV in routine immunization schedule at least for 5 years after OPV withdrawal (noting that countries with polio essential facilities will need to maintain IPV immunisation for at least the lifetime of these facilities). The WG will discuss future immunization policy in greater depth and detail at the next WG meeting.
- The WG agreed that countries should consider an additional dose of IPV into RI before global OPV withdrawal with the aim of achieving at least 90% seroconversion, but that the more detailed recommendations (e.g. the timeframe, schedule and dosing) will be further discussed during the next working group meeting. The discussions would include:
 - A comprehensive review of two-dose IPV schedule data
 - Analysis of feasibility of fractional IPV dose (e.g. operational feasibility, cost, wastage)
 - A cost-effectiveness analysis with two full or fractional IPV doses after the OPV cessation

Topic 5: iVDPV epidemiology and surveillance strategy

The WG received an update on the current known epidemiology of immunodeficiency-related vaccine-derived poliovirus (iVDPV) cases. Currently, there are 108 iVDPV patients in the WHO registry, many of which stopped excreting iVDPVs. The registry shows a substantial increase in reported cases that reflect increased surveillance efforts. Modelling and the registry suggest iVDPV prevalence characterized by two divergent trends – an increase in iVDPVs detected from middle-income countries (in part due to improved treatment of patients with primary immunodeficiencies (PIDs)) and a decrease from high-income countries (attributed to increasing use of IPV-only in these countries)). In terms of geographic distribution, there is clustering in the Middle East – possibly due to specific surveillance activities initiated by EMRO and higher rates of consanguinity. There is thought to be substantial underreporting, particularly for iVDPV cases without acute flaccid paralysis. Type 2 polioviruses account for the majority (~70%) of iVDPV cases. These iVDPVs may constitute a significant risk in triggering outbreaks among under-immunized populations post-OPV cessation. This risk appears to be concentrated in large and middle-income countries (e.g. India, Nigeria, Indonesia, and Egypt). The median duration of type 2 excretion decreased from 1.5-3.0 years during 1962, to 2011 and 1.0-1.3 years during 2011 to 2016.

The WG then reviewed the surveillance strategy for iVDPV case detection. Currently, there is no routine surveillance system to detect patients with PID in low/middle income countries. The WHO proposes to expand the AFP surveillance system for iVDPV cases, by identifying PID cases with a screening case definition for 'suspected PID' as part of AFP surveillance. Initially, the expansion will be implemented as a pilot test in up to five countries in the Middle East in 2016.

WG decisions/recommendations

- The WG commended the progress in detecting and analysing more iVDPV patients. It endorsed the proposed approach and pilot test to expand AFP surveillance system to detect more iVDPV patients.

Summary and next steps for the SAGE Working Group

The results of the WG will be presented at the October SAGE meeting for further discussions. In addition, the WG will continue to provide technical oversight on major areas, such as:

- Progress towards elimination of WPV and cVPDV
- Polio vaccine supply issues
- Risk mitigation strategy before the OPV cessation (e.g. bOPV campaigns before the cessation, detection of iVDPV cases)
- Future immunization policy (e.g. the timeframe, schedule and dosing)



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Contents

- 397 Fractional-dose inactivated poliovirus vaccination campaign, Telangana state, India, June 2016
- 403 Monthly report on dracunculiasis cases, January–May 2016

Sommaire

- 397 Campagne de vaccination par une dose fractionnée de poliovirus inactivé, État du Telangana (Inde), juin 2016
- 403 Rapport mensuel des cas de dracunculose, janvier-mai 2016

Fractional-dose inactivated poliovirus vaccination campaign, Telangana state, India, June 2016

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Campagne de vaccination par une dose fractionnée de poliovirus inactivé, État du Telangana (Inde), juin 2016

Sunil Bahl,^a Harish Verma,^b Pankaj Bhatnagar,^c Pradeep Haldar,^d Asish Satapathy,^c K N Arun Kumar,^c Jennifer Horton,^b Estivariz F. Concepcion,^e Abhijeet Anand,^e et Roland Sutter^b

Introduction

Wild poliovirus type 2 was declared eradicated in September 2015.¹ As part of a globally-synchronized effort to withdraw Sabin poliovirus type 2 vaccine, India switched from use of trivalent oral poliovirus vaccine (tOPV) to bivalent type 1 and 3 OPV (bOPV) in April 2016. Concurrently, inactivated poliovirus vaccine (IPV) was introduced to the routine immunization programme to maintain an immunity base that would mitigate the number of paralytic cases in the event of epidemic transmission of poliovirus type 2.^{2,3} After cessation of type 2 Sabin vaccine use, any reported vaccine-derived poliovirus type 2 (VDPV2) would be treated as a public health emergency and may need outbreak response with monovalent type 2 oral vaccine and/or IPV.⁴ In response to an isolation of VDPV2 from a sewage sample taken in Telangana state, India conducted a mass campaign using an intradermal fractional dose (0.1 ml) of IPV (fIPV) in June 2016. Over a period of 6 days, the campaign vaccinated 311 064 children aged from 6 weeks to 3 years. Reaching an estimated coverage of 94%, this indicated that, with

Introduction

L'éradication du poliovirus sauvage de type 2 a été déclarée en septembre 2015.¹ Dans le cadre de l'effort synchronisé à l'échelle mondiale de retrait du poliovirus de type 2 Sabin, l'Inde est passée de l'utilisation du vaccin antipoliomyélique oral trivalent (VPOt) à celle du vaccin antipoliomyélique bivalent types 1 et 3 (VPOb) en avril 2016. Dans le même temps, le vaccin antipoliomyélique inactivé (VPI) a été introduit dans le programme de vaccination systématique pour maintenir une base immunitaire capable de limiter le nombre de cas paralytiques dans l'éventualité d'une transmission épidémique du poliovirus de type 2.^{2,3} Après l'arrêt de l'utilisation du vaccin préparé à partir de la souche Sabin 2, toute détection notifiée d'un poliovirus dérivé d'une souche vaccinale de type 2 (PVDV2) sera traitée comme une urgence de santé publique et pourra nécessiter une riposte à la flambée à l'aide du vaccin antipoliomyélique oral monovalent de type 2 et/ou du VPI.⁴ En réponse à l'isolement d'un PVDV2 dans un échantillon d'eaux usées dans l'État du Telangana, l'Inde a mené une campagne de vaccination de masse à l'aide d'une dose fractionnée intradermique (0,1 ml) de VPI (VPIf) en juin 2016. Cette campagne a

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¹ Adams A, Salisbury DM. Eradicating polio. Science, New York. 2015, Nov 6;350(6261):609.

² The Global Polio Eradication Initiative. Polio Eradication and Endgame Strategic Plan 2013–2018. Geneva, Switzerland, 2013. Available at: <http://www.polioeradication.org/resource-library/strategyandwork.aspx>; accessed August 2016.

³ See No. 12, 2016, pp. 145–168.

⁴ The Global Polio Eradication Initiative. Responding to a Poliovirus Event and Outbreak. Geneva, Switzerland 2016 [cited 27 July 2016]. Available at: www.polioeradication.org/Portals/0/Document/Resources/PolioEradicators/1a.PolioOutbreakGuideline201604part2.pdf; accessed August 2016.

¹ Adams A, Salisbury DM. Eradicating polio. Science, New York. 2015, Nov 6;350(6261):609.

² Plan Stratégique pour l'éradication de la poliomyélite et la phase finale 2013 – 2018. Genève, Suisse, 2013. Disponible à l'adresse: <http://www.polioeradication.org/resourcelibrary/strategyandwork.aspx>; consulté en août 2016.

³ Voir N° 12, 2016, p. 145-168.

⁴ Initiative mondiale pour l'éradication de la poliomyélite. Riposter à un événement ou à une épidémie de poliovirus. Genève (Suisse), 2016 [cité le 27 Juillet 2016]. Disponible à l'adresse: www.polioeradication.org/Portals/0/Document/Resources/PolioEradicators/1a.PolioOutbreakGuideline201604part2.pdf; consulté en août 2016.

appropriate preparation, an emergency response of fIPV could be implemented promptly and successfully without adverse consequences. The lessons learned can be applied to the successful implementation of future outbreak responses using fIPV.

Background

On 7 June 2016, a VDPV2 isolate with 10 nucleotide changes from the corresponding OPV strain was reported in an environmental surveillance sample collected from a sewage site on 16 May 2016. This sample was collected from Amberpet sewage treatment plant, which receives sewage from parts of Hyderabad and Rangareddy districts of Telangana state (*Map 1*). No cases of acute flaccid paralysis caused by poliovirus were reported and an active search of medical records in health-care facilities found no unreported flaccid paralysis cases in the prior 6 months in either of the 2 districts. The last reported wild poliovirus case in Telangana state was in 2007 and no VDPV had been reported from any sampling site since the initiation of environmental sampling in Hyderabad district in April 2016.

Following a standard outbreak review protocol for a VDPV2 event,⁴ and after a joint national (Government of India and Telangana state) and international (Global Polio Eradication Initiative (GPEI)) review, a decision was made to conduct an outbreak response campaign using a fractional IPV dose (one fifth of a regular intramuscular (IM) dose) administered intradermally. Clinical trials have demonstrated that fIPV is highly immunogenic and boosts the immune response.^{5,6} The use of fIPV also stretches limited supplies of IPV by using only one fifth of a regular IM dose of IPV for vaccination. The target group for the fIPV campaign were children aged from 6 weeks to 3 years. The campaign was limited to areas from which sewage drains to the Amberpet sewage treatment plant and which were considered at high risk of a potential outbreak of circulating vaccine-derived poliovirus (cVDPV), based on coverage of routine immunization and the quality of prior polio campaigns (such as in Hyderabad district); it was also conducted in the adjoining high-risk slum and migrant populations of Rangareddy district.

The campaign was implemented using a “fixed site” approach, in which a convenient location is selected in a neighbourhood to which parents or caretakers can bring children for vaccination. This is in contrast to the

permis de vacciner 311 064 enfants âgés de 6 semaines à 3 ans, en l'espace de 6 jours. En permettant d'obtenir un taux de couverture estimé de 94%, l'expérience a montré que, moyennant une préparation appropriée, une riposte d'urgence utilisant le VPIf pouvait être mise en œuvre rapidement et avec succès, sans conséquences préjudiciables. Les enseignements tirés peuvent s'appliquer à la mise en œuvre réussie des futures ripostes à une flambée à l'aide du VPIf.

Considérations générales

Le 7 juin 2016, un isolement de PVDV2 présentant 10 changements nucléotidiques par rapport à la souche de VPO correspondante a été notifié dans un échantillon destiné à la surveillance environnementale prélevé sur un site de prélèvement d'eaux usées le 16 mai 2016. Cet échantillon avait été recueilli dans l'installation de traitement des eaux usées d'Amberpet, qui reçoit les effluents domestiques des districts d'Hyderabad et Rangareddy dans l'État du Telangana (*Carte 1*). Aucun cas de paralysie flasque aiguë causée par un poliovirus n'a été signalé et une recherche active dans les dossiers médicaux des établissements de soins n'a relevé aucun cas de paralysie flasque aiguë non notifié pendant les 6 mois précédents dans les 2 districts. Le dernier cas de poliovirus sauvage notifié dans l'État du Telangana datait de 2007 et aucun PVDV n'avait été signalé en provenance d'un site de prélèvement depuis la mise en place du prélèvement environnemental dans le district de Hyderabad en avril 2016.

En appliquant un protocole standard d'examen des flambées pour un événement lié à un PVDV2⁴ et après un examen conjoint aux niveaux national (Gouvernements de l'Inde et de l'État du Telangana) et international (Initiative mondiale pour l'éradication de la poliomyélite [IMEP]), la décision a été prise de mener une campagne de riposte à cette flambée à l'aide d'une dose fractionnée de VPI (VPIf, soit un cinquième de la dose intramusculaire (IM) habituelle), administrée par voie intradermique. Des essais cliniques ont démontré que le VPIf est hautement immunogène et renforce la réponse immunitaire.^{5,6} Le recours au VPIf permet aussi de multiplier le nombre de bénéficiaires des approvisionnements en VPI en utilisant seulement un cinquième de la dose IM habituelle pour la vaccination par le VPI. Le groupe cible de la campagne utilisant le VPIf était constitué d'enfants âgés de 6 semaines à 3 ans. Cette campagne a été limitée aux zones dont les eaux usées alimentent l'installation de traitement d'Amberpet et qui sont considérées comme à haut risque de flambée de poliovirus circulants dérivés d'une souche vaccinale (PVDVc), compte tenu de la couverture obtenue par la vaccination systématique et de la qualité des campagnes antipoliomyélitiques antérieures (ville/district d'Hyderabad, par exemple); elle a aussi été conduite parmi des populations migrantes ou vivant dans des bidonvilles à haut risque adjacents du district de Rangareddy.

La mise en œuvre de la campagne a fait appel à un «site de vaccination fixe» (lieu choisi dans le voisinage pour ses caractéristiques pratiques et sur lequel les parents/les aidants peuvent amener les enfants pour les faire vacciner). Cette

⁵ Estivariz CF, Jafari H, Sutter RW, John TJ, Jain V, Agarwal A, et al. Immunogenicity of supplemental doses of poliovirus vaccine for children aged 6–9 months in Moradabad, India: a community-based, randomised controlled trial. *Lancet Infect Dis.* [Research Support, Non-U.S. Gov't]. 2012 Feb;12(2):128–135.

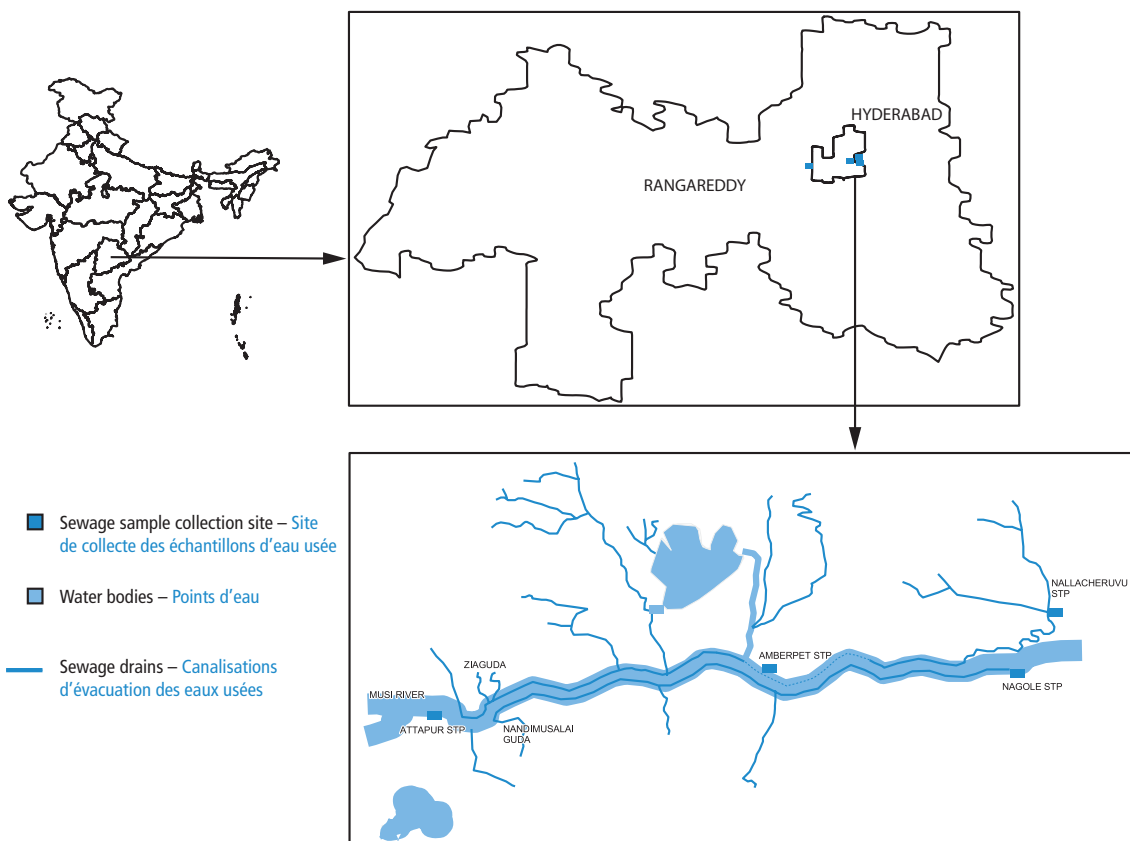
⁶ Resik S, Tejeda A, Mach O, Fonseca M, Diaz M, Alemany N, et al. Immune responses after fractional doses of inactivated poliovirus vaccine using newly developed intradermal jet injectors: a randomized controlled trial in Cuba. *Vaccine.* 2015 Jan 3;33(2):307–313.

⁵ Estivariz CF, Jafari H, Sutter RW, John TJ, Jain V, Agarwal A, et al. Immunogenicity of supplemental doses of poliovirus vaccine for children aged 6–9 months in Moradabad, India: a community-based, randomised controlled trial. *Lancet Infect Dis.* [Research Support, Non-U.S. Gov't]. 2012 Feb;12(2):128–135.

⁶ Resik S, Tejeda A, Mach O, Fonseca M, Diaz M, Alemany N, et al. Immune responses after fractional doses of inactivated poliovirus vaccine using newly developed intradermal jet injectors: a randomized controlled trial in Cuba. *Vaccine.* 2015 Jan 3;33(2):307–313.

Map 1 Sewage sample collection sites, Hyderabad and Rangareddy districts, India, May 2016

Carte 1 Sites de collecte des échantillons d'eau usée, districts de Hyderabad et Rangareddy, Inde, mai 2016



STP = sewage treatment plant. – Unité de traitement des eaux usées.

house-to-house approach used for OPV campaigns, during which OPV is administered to target children directly in their home or at other points where target children are encountered, such as at bus stops or at public markets. The campaign was implemented from 20–25 June 2016, well within the recommended maximum 14 days interval to conduct a response since the initial confirmation of VDPV.⁴

Campaign planning and implementation

Twenty-nine surveillance medical officers of the India WHO National Polio Surveillance Project were deployed to support the development of campaign microplans and to conduct pre-campaign training and campaign monitoring. Existing microplans of prior OPV campaigns were adapted for IPV supplementary immunization activities. A rapid house-to-house survey was undertaken to enumerate all eligible children and inform families of the IPV campaign. The target population was estimated to be 291 305.

démarche s'oppose à la stratégie de visite porte à porte, appliquée pour les campagnes utilisant le VPO, qui prévoit l'administration du VPO aux enfants visés directement à leur domicile ou en d'autres points où l'on peut les rencontrer, comme des arrêts de bus ou des marchés publics. La campagne a été mise en œuvre du 20 au 25 juin 2016, dans l'intervalle de 14 jours au maximum après la confirmation initiale d'un cas de PVDV recommandé pour organiser une riposte.⁴

Planification et mise en œuvre de la campagne

Vingt-neuf médecins, chargés de la surveillance du Projet national de surveillance de la poliomyélite de l'OMS en Inde, ont été déployés dans le but d'appuyer la mise au point des microplans de campagne et de mener la formation préliminaire à cette campagne et le suivi de celle-ci. Les microplans déjà établis pour les campagnes antérieures ont été adaptés pour les activités de vaccination supplémentaire à l'aide du VPI. Une enquête rapide porte à porte a été entreprise pour dénombrer l'ensemble des enfants pouvant bénéficier de cette vaccination et informer les familles de la campagne vaccinale par le VPI à venir. La population cible a été estimée à 291 305 enfants.

A total of 5373 immunization sessions were organized over 6 days (Table 1). The number of daily sessions varied from 719 to 1227. A total of 1038 vaccinators supported implementation of the campaign, with 638 being mobilized from neighbouring districts. Each session was managed by a team of at least 4 members and included 1 vaccinator (an auxiliary nurse midwife [ANM]), 2 community mobilizers and 1 volunteer. For routine immunization, ANMs administered all injectable vaccines. A one-day training session was organized to inform and instruct all vaccination staff.

Au total, 5373 sessions de vaccination ont été organisées sur 6 jours (Tableau 1). Le nombre de sessions par jour a varié de 719 à 1227. Mille trente-huit vaccinateurs au total ont participé à la mise en œuvre de la campagne, parmi lesquels 638 avaient été mobilisés dans des districts voisins. Chaque session a été gérée par une équipe de 4 membres au moins, comprenant un vaccinateur (une infirmière sage-femme auxiliaire [ANM]), 2 mobilisateurs communautaires et 1 volontaire. Aux fins de la vaccination systématique, les ANM administrent tous les vaccins injectables. Une session de formation d'une journée a été organisée pour informer et instruire tout le personnel de vaccination.

Table 1 **Fractional inactivated poliovirus vaccination: reported children targeted versus vaccinated, Telangana, India, 20–25 June 2016**
Tableau 1 **Vaccination par une dose fractionnée de poliovirus inactivé: estimation du nombre d'enfants visés contre nombre d'enfants vaccinés, Telangana, Inde, 20-25 juin 2016**

District	No. of vaccination sessions conducted – Nombre de sessions de vaccination organisées	Children targeted (6 weeks–3 years) – Enfants visés	Total children reported vaccinated with fIPV ^a – Nombre total d'enfants rapportés comme vaccinés avec le VPIf ^a		Children vaccinated per day – Enfants vaccinés par jour	
			Number – Nombre	Percentage – Pourcentage	Median – Valeur médiane	Range – Plage de variation
Hyderabad	4360	231 482	200 480	87	68	10–102
Rangareddy	1013	59 823	110 584	185	87	24–148
Total	5373	291 305	311 064	107	73	10–148

^a fIPV = fractional dose of inactivated poliovirus vaccine, equivalent to 1/5 of an intramuscular dose. – VPIf: dose fractionnée de poliovirus inactivé, soit un cinquième de la dose intramusculaire habituelle.

The IPV vials used in the campaign were 10 IM-dose vials manufactured by the Indian manufacturer Shantha Biotech (ShanIPV), with 0.1 ml withdrawn for each fIPV vaccination. Therefore, each 10 IM dose vial could potentially vaccinate 50 children with fIPV. The multi-dose vial policy of the Indian immunization programme permitted use of open vials for up to 28 days from the date of first use; partially-used opened vials returned at the end of each campaign day were used first as a priority the following morning. A 0.1 ml dose of fIPV was administered intradermally on the lateral aspect of the right upper arm using an auto-disable BCG⁷ needle and syringe (with a 0.1 ml mark). This is a “fixed system” whereby the needle cannot be removed from the syringe and vaccine wastage within the syringe is thus reduced. Following vaccination, the nail of the left little finger of each vaccinee was marked with an indelible marker pen. Social mobilization for the campaign was conducted through print and electronic media, posters, invitation slips to parents of eligible children indicating the day and place of immunization sessions, banners, microphone announcements and community mobilizers.

Parents/caregivers were asked to report any adverse events occurring within a week of receiving the vaccine, including illness, hospitalizations or deaths.

Ont servi à la campagne des flacons de VPI de 10 doses IM fabriqués par le producteur indien Shantha Biotech (ShanIPV), dans lesquels on a prélevé 0,1 ml pour chaque vaccination par le VPIf. Par conséquent, chaque flacon contenant 10 doses IM pourrait potentiellement servir à vacciner 50 enfants avec le VPIf. La politique relative aux flacons multidoses du programme de vaccination indien a permis d'utiliser les flacons ouverts jusqu'à 28 jours après la première utilisation; les flacons ouverts, partiellement utilisés, retournés à la fin de chaque journée de campagne, étaient débités en priorité le matin suivant. Une dose de 0,1 ml de VPIf a été administrée par voie intradermique sur la face latérale du bras droit, à l'aide d'une aiguille et d'une seringue autobloquantes utilisées pour le BCG⁷ (comportant une graduation pour 0,1 ml). Ce dispositif est un «système fixe» qui ne permet pas le retrait de l'aiguille de la seringue et qui réduit le gaspillage de vaccin à l'intérieur de la seringue. Après la vaccination, l'ongle du petit doigt gauche de chaque enfant vacciné est marqué avec un marqueur indélébile. La mobilisation sociale en faveur de la campagne a fait appel à des médias imprimés et électroniques, à des prospectus d'invitation pour les parents des enfants susceptibles d'être vaccinés (qui indiquaient le jour et le lieu des sessions de vaccination), à des banderoles, à des annonces au mégaphone et à des mobilisateurs communautaires.

Il a été demandé aux parents comme aux soignant de signaler tout effet secondaire survenant dans la semaine suivant l'administration du vaccin, y compris les cas de maladie, les hospitalisations ou les décès.

⁷ Bacillus Calmette–Guérin.

⁶ Bacille de Calmette–Guérin.

Campaign monitoring

At least one campaign monitor was assigned to each of the 25 blocks or administrative divisions in the districts of Hyderabad and Rangareddy. Areas selected for monitoring were known locations of residence of disenfranchised, mobile or migrant populations, or those of other groups for which lower-than-average routine immunization coverage was reported. A total of 958 (18%) vaccination sessions were monitored over the 6 campaign days (Table 2). All monitored team sessions were organized as planned and 96% of the monitored teams used the same vaccinator as listed in the microplan. Of the monitored teams, 97% had adequate supplies to conduct a vaccination session. Due to high demand for fIPV, particularly on the first 2 days of the campaign, 6% of monitored teams reported a shortage of IPV vials at some time during their session. Monitors observed no frozen IPV vials, and no vials with vaccine vial monitors at the discard point being used, implying an overall appropriate maintenance of the cold chain.

Suivi de la campagne

Au moins un contrôleur de campagne a été affecté à chacun des 25 blocs ou divisions administratives des districts d'Hyderabad et Rangareddy. Les zones sélectionnées pour faire l'objet d'un suivi étaient connues comme lieux de résidence pour des populations privées de leurs droits, mobiles ou migrantes, ou abritaient des groupes signalés comme disposant d'une couverture vaccinale plus faible que la couverture habituelle. Au total, 958 (18%) des sessions de vaccination ont été suivies sur les 6 jours de campagne (Tableau 2). Toutes les sessions ayant fait l'objet d'un suivi ont été organisées comme prévu et 96% des équipes suivies disposaient du vaccinateur indiqué dans le microplan. Parmi ces équipes, 97% avaient accès à des approvisionnements suffisants pour mener une session de vaccination. En raison de la forte demande en VPIf, en particulier pendant les 2 premiers jours de la campagne, 6% des équipes suivies ont signalé une pénurie de flacons de VPI à un moment donné de leur session. Aucun flacon de VPI gelé n'a été observé ni aucun flacon porteur d'une pastille de contrôle indiquant la nécessité de sa mise au rebut en cours d'utilisation, ce qui supposait un maintien global approprié de la chaîne du froid.

Table 2 **Fractional inactivated poliovirus vaccination campaign: monitoring sessions and children Telangana, India, June 2016**
Tableau 2 **Campagne de vaccination par une dose fractionnée de poliovirus inactivé: suivi des sessions et des enfants, Telangana, Inde, juin 2016**

District	Campaign monitoring – Suivi de la campagne				Post-campaign evaluation – Evaluation post-campagne	
	No. of monitors – Nbre de contrôleurs	No. of sessions monitored (%) – Nbre de sessions suivies (%)	% sessions with vaccinators same as microplan – % des sessions disposant des vaccinateurs prévus par le microplan	% sessions with adequate vaccine/syringes – % des sessions disposant de vaccins/seringues en quantités suffisantes	No. of children checked by monitors post-campaign for vaccination status – Nbre d'enfants dont le statut vaccinal a été vérifié par les contrôleurs après la campagne	% children found vaccinated by monitors post-campaign – % d'enfants trouvés vaccinés par les contrôleurs après la campagne ^a
Hyderabad	30	661(15)	95	98	1862	96
Rangareddy	16	297 (29)	98	94	959	91
Total	46	958 (18)	96	97	2821	94

^a Based on examination of finger marking. – Basé sur l'examen des marques sur les doigts.

On the first day of the campaign a median of 48 fIPV doses (range: 41–50) were extracted from each IPV vial. Monitors noted there was no vaccine leakage from the vial caps during monitored sessions. In 93% of observed children, a bleb, indicative of intradermal delivery of fIPV, was observed immediately after vaccination. A median of 73 children (10–148) was vaccinated in each session on day 1 of the campaign.

Le premier jour de la campagne, un nombre médian de 48 doses de VPIf (plage de variation: 41-50) ont pu être extraites de chaque flacon de VPI. Les contrôleurs ont également noté qu'il n'y avait pas de fuite de vaccin provenant du dispositif de fermeture des flacons pendant les sessions ayant fait l'objet d'un suivi. Chez 93% des enfants observés, une bulle, indiquant la délivrance intradermique du VPIf, a été constatée immédiatement après la vaccination. Le premier jour de la campagne, il a été vacciné un nombre médian de 73 enfants (plage de variation: 10-148) par session.

Post campaign evaluation and coverage

A total of 311 064 children were reported vaccinated during the campaign: 107% of the initially-estimated target of 291 305 children (Table 1). Reported coverage in Hyderabad district was 87% of the estimated target, while in Rangareddy district the number of children

Évaluation postcampagne et couverture

Au total, 311064 enfants ont été signalés comme vaccinés pendant la campagne, soit 107% de la population cible initialement estimée de 291305 enfants (Tableau 1). La couverture rapportée dans le district de Hyderabad atteignait 87% de la cible estimée, tandis que dans le district de Rangareddy, près de

vaccinated was almost double that initially estimated (185%). The high reported coverage in Rangareddy district is attributed to a large number of children from non-targeted areas adjacent to the targeted areas who received vaccine during the campaign. A post campaign assessment was conducted by 46 monitors to determine the likely number of missed children in a given location. The monitors prioritized known locations of residence of disenfranchised, migrant or mobile populations. A total of 2821 children were randomly checked as part of a post-coverage monitoring survey and 94% of children assessed (through finger marking) were found to have received fIPV during the campaign (Table 2). Key reasons for non-vaccination include the child being unavailable on the day of vaccination (29%); the child being sick (21%); a lack of parental awareness (16%); fear of injection (2%); and hesitancy and refusal (6.2%).

A total of 4 non-serious adverse events were reported within a week after receipt of fIPV; none was deemed related to vaccination.

Discussion

Although vaccination campaigns with injectable vaccines have been conducted for other diseases, this was the first global campaign to use fIPV, requiring vaccinators experienced in the technique of intradermal injection. Overall, this emergency response to a reported VDPV2 event demonstrated that it is feasible to plan and implement a fIPV campaign within 14 days of the reported event and to achieve high reported coverage. Critical elements for the successful implementation of the fIPV campaign in Telangana state, India were strong government leadership at the national and state level, well-coordinated technical and operational support from GPEI partners, clearly-defined standard operating procedures for outbreak response, and prior experience in implementing OPV campaigns.

Lessons learned from this campaign are likely to aid India and other countries in the successful implementation of future fIPV and other emergency campaigns using injectable vaccines. Meticulous planning ensured a sufficient number of strategically-located vaccination sites and vaccinators with prior experience in intradermal administration of vaccines as well as rapid refresher training. The planning and post-campaign monitoring assisted in achieving sound injection practices and high reported coverage.

An emergency operations centre set-up by the government, with strong support from GPEI partners, coordinated the overall emergency operation. Modern technologies, such as group messaging ensured rapid communication among all stakeholders. Progress in all sectors of the campaign area was shared real-time during the preparatory and implementation phases, as were challenges and barriers, and this ensured faster collective solutions.

2 fois plus d'enfants que le nombre initialement estimé (185%) ont reçu le vaccin. La forte couverture rapportée dans le district de Rangareddy est attribuée à la vaccination pendant la campagne d'un grand nombre d'enfants issus des zones adjacentes non visées. Une évaluation postcampagne a été réalisée par 46 contrôleurs pour estimer le nombre probable d'enfants laissés de côté en un lieu donné. Les contrôleurs ont donné la priorité à des zones dont on savait qu'elles abritaient des populations privées de leurs droits, migrantes ou mobiles. Au total, 2821 enfants ont fait l'objet d'un contrôle aléatoire dans le cadre de l'enquête de suivi postcouverture et les contrôleurs ont constaté que, globalement, 94% des enfants évalués avaient reçu le vaccin VPIf pendant la campagne d'après le marquage apparaissant ou non sur leur ongle (Tableau 2). Parmi les principaux motifs de l'absence de vaccination, figuraient l'indisponibilité de l'enfant le jour de la vaccination (29%), la présence chez lui d'une maladie (21%), le manque de sensibilisation parentale (16%), la crainte de l'injection (2%) ainsi que l'hésitation et le refus (6,2%).

Au total, 4 manifestations indésirables sans gravité ont été signalées dans la semaine suivant la réception du VPIf et ont été jugées sans lien avec la vaccination.

Discussion

Bien que des campagnes de vaccination par des vaccins injectables aient été menées pour d'autres maladies, celle-ci a été la première campagne mondiale utilisant le VPIf, ce qui a nécessité des vaccinateurs expérimentés dans la technique d'injection intradermique. Globalement, cette riposte d'urgence à un événement lié à un PVDV2 notifié a démontré qu'il était faisable de planifier et de mettre en œuvre une campagne utilisant le VPIf dans le délai de 14 jours imparti après l'événement notifié et d'obtenir une forte couverture rapportée. Les éléments déterminants dans le succès de cette campagne d'administration du VPIf dans l'État du Telangana (Inde) ont été une direction gouvernementale forte au niveau du pays et de l'État, un soutien technique et opérationnel bien coordonné de la part des partenaires de l'IMEP, des procédures opératoires standardisées clairement définies pour la riposte à la flambée et une expérience antérieure dans la mise en œuvre des campagnes utilisant le VPO.

Un certain nombre d'enseignements tirés de cette expérience aideront probablement l'Inde et d'autres pays à mettre en œuvre avec succès les futures campagnes de vaccination par le VPIf ainsi que des campagnes d'urgence avec d'autres vaccins injectables. Une planification méticuleuse, visant à garantir un nombre suffisant de sites de vaccination stratégiquement situés et de vaccinateurs disposant d'une expérience antérieure dans l'administration intradermique de vaccins, couplée à une remise à niveau rapide. La planification et le suivi postcampagne ont contribué à l'application de bonnes pratiques d'injection et à l'obtention d'une forte couverture.

Un centre d'opérations d'urgence mis sur pied par le Gouvernement, et solidement soutenu par les partenaires de l'IMEP, a coordonné l'ensemble de l'intervention d'urgence. Des technologies modernes, comme la messagerie de groupe, se sont révélées très utiles pour assurer une communication rapide entre toutes les parties prenantes. Les progrès dans l'ensemble des secteurs de la zone couverte par la campagne ont été communiqués en temps réel pendant les phases de préparation et de mise en œuvre, tout comme l'ont été les difficultés et les obstacles, afin de parvenir plus rapidement à des solutions collectives permettant de les surmonter.

The sharing of accurate and timely information between public health workers and the media helped in the development of a positive partnership. Extensive publicity of the campaign by the media, a perceived threat of the return of polio and the non-availability of IPV in the private sector, all contributed to high community participation at vaccination sites during the campaign and high vaccination coverage. Nonetheless, there was some inaccurate media reporting and the early identification of a public health spokesperson and the timely development of key messages would be important considerations for future similar campaigns.

One unanticipated problem was that the number of children identified during pre-campaign surveys did not correspond with the number of children who reported to the vaccination site to receive fIPV. Therefore, when planning for a time-sensitive outbreak response, resource-intensive pre-campaign surveys should be avoided. Instead, available resources should be used to conduct focus group discussions to guide the microplanning process and communication strategies. Robust mobilization efforts carried out by community health workers and volunteers on the day of the campaign were highly effective in achieving a high vaccination coverage. Any sizeable vaccination campaign to be conducted in an emergency situation with an injectable vaccine and requiring a large number of trained vaccinators brought in from districts outside the targeted area needs to be anticipated in response plans for future similar campaigns.

Conclusion

The experience in Telangana state (India) demonstrates that intradermal fIPV administration is possible in an emergency campaign setting. The operational and logistical challenges to achieving high vaccination coverage during an fIPV campaign can be overcome with the comprehensive and coordinated efforts of government and partners.

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La communication en temps utile et avec exactitude des informations entre les agents de santé du secteur public et les médias a participé au développement d'un partenariat positif. La large publicité faite par les médias de masse à la campagne, la menace perçue d'un retour de la poliomyélite et l'indisponibilité du VPI dans le secteur privé ont contribué à la forte participation des communautés sur les sites de vaccination pendant la campagne et à l'obtention d'un taux de couverture élevé. Les médias ont néanmoins rapporté certaines informations erronées et la désignation précoce d'un porte-parole pour la santé publique et la mise au point en temps utile de messages clés seront importants pour les futures campagnes de ce type.

L'un des problèmes ayant été anticipé était que le nombre d'enfants identifiés lors des enquêtes préalables à la campagne ne correspondait pas au nombre d'enfants recensés comme vaccinés par le VPIf sur le site de vaccination. Par conséquent, pour la planification d'une riposte à une flambée sensible au facteur temps, on évitera les enquêtes préalables, fortes consommatrices de ressources. Les ressources disponibles devront au contraire être employées à l'organisation de discussions en groupe restreint en vue de guider le processus de microplanification et les stratégies de communication. Les efforts importants de mobilisation par des agents de santé communautaires et des volontaires lors de la campagne se sont révélés hautement efficaces pour obtenir une forte couverture. Une campagne de vaccination de grande ampleur avec un vaccin injectable, menée dans une situation d'urgence, exige de réunir dans la zone visée un grand nombre de vaccinateurs formés provenant d'autres districts; ce qui doit être anticipé dans les plans de riposte des futures campagnes de ce type.

Conclusion

L'expérience acquise dans l'État du Telangana (Inde) a montré que l'administration par voie intradermique du VPIf était possible dans le contexte d'une campagne d'urgence. Les difficultés opérationnelles et logistiques peuvent être surmontées pour obtenir une forte couverture par cette campagne moyennant une solide coordination des gouvernements et des partenaires.

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Monthly report on dracunculiasis cases, January–May 2016

In order to monitor the progress accomplished towards dracunculiasis eradication, district-wise surveillance indicators, a line list of cases and a line list of villages with cases are sent to WHO by the national dracunculiasis eradication programmes. Information below is summarized from these reports. ■

RELEVÉ ÉPIDÉMIOLOGIQUE HEBDOMADAIRE, N° 34, 26 AOÛT 2016

Rapport mensuel des cas de dracunculose, janvier-mai 2016

Afin de suivre les progrès réalisés vers l'éradication de la dracunculose, les programmes nationaux d'éradication de la dracunculose envoient à l'OMS des indicateurs de surveillance des districts sanitaires, une liste exhaustive des cas ainsi qu'une liste des villages ayant signalé des cas. Les renseignements ci-dessous sont résumés à partir de ces rapports. ■

403

Update on Vaccine-Derived Polioviruses — Worldwide, January 2015–May 2016

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In 1988, the World Health Assembly resolved to eradicate poliomyelitis worldwide (1). One of the main tools used in polio eradication efforts has been the live, attenuated, oral poliovirus vaccine (OPV) (2), an inexpensive vaccine easily administered by trained volunteers. OPV might require several doses to induce immunity, but provides long-term protection against paralytic disease. Through effective use of OPV, the Global Polio Eradication Initiative (GPEI) has brought wild polioviruses to the threshold of eradication (1). However, OPV use, particularly in areas with low routine vaccination coverage, is associated with the emergence of genetically divergent vaccine-derived polioviruses (VDPVs) whose genetic drift from the parental OPV strains indicates prolonged replication or circulation (3). VDPVs can emerge among immunologically normal vaccine recipients and their contacts as well as among persons with primary immunodeficiencies (PIDs). Immunodeficiency-associated VDPVs (iVDPVs) can replicate for years in some persons with PIDs. In addition, circulating vaccine-derived polioviruses (cVDPVs) (3) can emerge in areas with low OPV coverage and can cause outbreaks of paralytic polio. This report updates previous summaries regarding VDPVs (4).

During January 2015–May 2016, five new cVDPV outbreaks were identified in Burma (Myanmar) (two cases), Guinea (seven cases), Laos (11 cases), Madagascar (10 cases), and Ukraine (two cases) (5), while cVDPV type 2 (cVDPV2) circulation in Nigeria and Pakistan decreased sharply. Twenty-one newly identified persons in 10 countries were found to excrete iVDPVs, and a patient in the United Kingdom was still excreting an iVDPV in 2015 after >29 years of chronic infection. Ambiguous VDPVs (aVDPVs), isolates that cannot be classified definitively, were found among immunocompetent persons and environmental samples in 19 countries.

Global eradication of wild poliovirus type 2 was declared in September 2015, and wild poliovirus type 3 has not been detected since 2012. Currently, wild poliovirus type 1 transmission has been identified only in Afghanistan and Pakistan. Because the majority of VDPV isolates that have emerged from OPV use in recent years are type 2, the World Health Organization coordinated the worldwide replacement of trivalent OPV (tOPV; Sabin types 1, 2, and 3) with bivalent OPV (bOPV; types 1 and 3) in April 2016, preceded by introduction of at least 1 dose of injectable inactivated poliovirus vaccine (IPV) into routine immunization schedules in countries with higher risk for VDPV2 emergence and spread (6).

Properties of VDPVs

VDPVs are polioviruses whose genetic divergence from the parental OPV strains indicates prolonged replication or circulation (3). Three poliovirus serotypes (PV1, PV2, and PV3) have been identified. Poliovirus isolates are grouped into three categories: wild polioviruses (WPVs), vaccine-related polioviruses (VRPVs), and vaccine-derived polioviruses (VDPV). WPVs are capable of sustained person-to-person transmission without genetic evidence of vaccine strain origin. VRPVs have limited divergence (<1% divergent [PV1 and PV3] or <0.6% divergent [PV2]) in the VP1 nucleotide sequences from the corresponding OPV strain. VDPVs are >1% divergent (for PV1 and PV3) or >0.6% divergent (for PV2) in VP1 sequences from the corresponding OPV strain (3). VDPVs are further classified as 1) cVDPVs, when evidence of person-to-person transmission in the community exists; 2) iVDPVs, when they are isolated from persons with PIDs; and 3) aVDPVs, when they are clinical isolates from persons with no known immunodeficiency and no evidence of transmission, or they are sewage isolates that are unrelated to other known VDPVs and whose source is unknown (3).

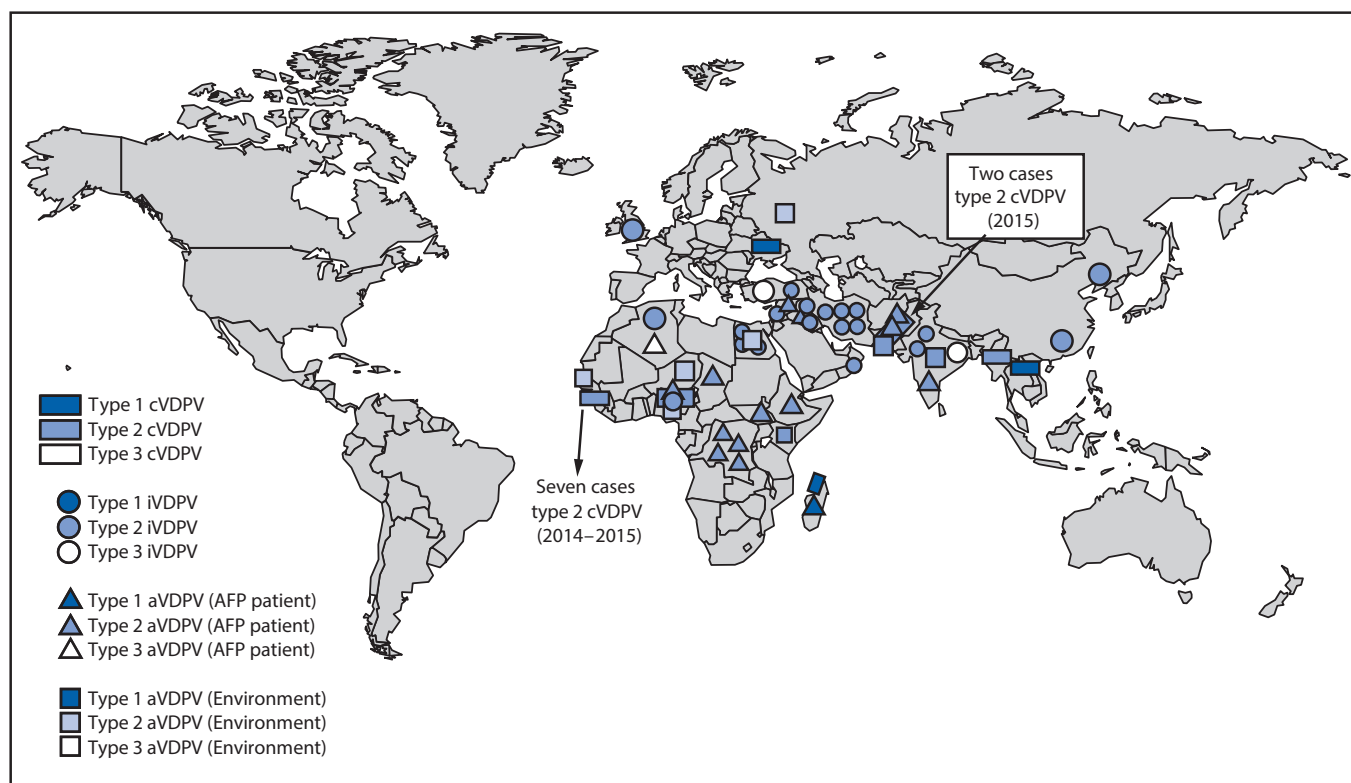
Virologic Testing for VDPVs

All poliovirus isolates are characterized by laboratories of the Global Polio Laboratory Network (4). VDPV screening is conducted using real-time reverse transcription–polymerase chain reaction (rRT-PCR) nucleic acid amplification, targeted to nucleotide substitutions that frequently revert to the parental WPV sequence during replication of OPV in the human intestine (7). Potential VDPVs identified by rRT-PCR screening are sequenced in the VP1 region for definitive analysis; the complete genome is sequenced if required for higher-resolution analysis.

Detection of cVDPVs

During January 2015–May 2016, the number of countries with detected cVDPV circulation increased from four to seven (Figure 1) (4). Outbreaks in South Sudan (cVDPV2) and Afghanistan (cVDPV2) appear to have been interrupted. Outbreaks of cVDPV2 in Pakistan and Nigeria have declined to very low incidence levels (4,8). New outbreaks were reported in Ukraine (cVDPV type 1 [cVDPV1], two cases), Burma (cVDPV2, two cases), Guinea (cVDPV2, seven cases), Laos (cVDPV1, 11 cases), and Madagascar (cVDPV1,

FIGURE 1. Vaccine-derived polioviruses (VDPVs) detected worldwide, January 2015–May 2016*



Abbreviations: cVDPV = circulating VDPV; iVDPV = immunodeficiency-associated VDPV; aVDPV = ambiguous VDPV; AFP = acute flaccid paralysis.

* Spread of cVDPVs followed the elimination of the corresponding serotype of indigenous wild poliovirus, but with continued introduction of oral poliovirus vaccine into communities with growing immunity gaps. All of the cVDPV outbreaks were detected first by the laboratory, using sequence data and evolutionary analyses.

10 cases) (Table). Among the 721 cVDPV cases detected worldwide during January 2006–May 2016, 681 (94%) were associated with cVDPV2, and 31 (4%) were associated with cVDPV1; however, during January 2015–May 2016, among 35 cVDPV cases, 23 (66%) were cVDPV1 (Table) (Figure 2).

Guinea. During 2015, seven cVDPV2s were isolated from patients aged <15 years with acute flaccid paralysis (AFP) in Kankan Province (up to 3% VP1 divergence). The first detected cVDPV2 associated with this outbreak was isolated from a patient in the same province with an August 2014 paralysis onset date.

Laos. Eight cVDPV1 cases in 2015 and three cases in 2016 were detected in three adjacent provinces (2.3%–3.9% VP1 divergence). The most recent case was reported in Fuang District of Vientiane Province, with paralysis onset in January 2016.

Madagascar. A cVDPV1 outbreak was initially detected in September 2014 in Analalava, Mahjanga Province, on the northwest coast; the virus circulated widely throughout the country during 2015. Genetically linked viruses were isolated in 2015; 10 AFP cases and 11 isolates were identified through

community-based surveillance, with VP1 nucleotide sequence divergence up to 3.3% from the parental OPV strain.

Burma (Myanmar). During April and October 2015, two related cVDPV2s (1.4%–1.7% VP1 divergence) were detected from two AFP cases in the same province; the most recent isolate was from an AFP case in Rakhine province with onset date October 5, 2015.

Nigeria. Low-level circulation in northern states continued during January 2015–May 2016 (4). Virus from the major cVDPV2 lineage group that first emerged in 2005 (8) was isolated from a sewage sample collected on March 4, 2015 (7.3% VP1 divergence). Virus from an independent cVDPV2 emergence (3.5% VP1 divergence from Sabin 2 and 2.2% divergence from its nearest relative), originating in Chad in 2012 (9), was isolated from sewage samples; the most recent positive sample was reported from Borno State on April 29, 2016 (10). In addition, one Kaduna State sewage isolate and an isolate from an AFP case were linked to the outbreak detected in 2014 (the most recent positive sample was reported on May 28, 2015 [1.4% VP1 divergence]) (4).

TABLE. Number of vaccine-derived polioviruses (VDPVs) detected, by classification and other selected characteristics — worldwide, January 2015–May 2016

Country	Year(s) detected*	Source†	Serotype	No. of isolates [§] January 2015–May 2016			VP1 divergence from Sabin OPV strain (%) [¶]	Routine OPV3 coverage (%)**	Estimated duration of VDPV replication ^{††}	Current status (date of last outbreak case, patient isolate, or environmental sample)
				No. of cases	No. of contacts	No. of non-AFP sources				
Circulating VDPVs (cVDPVs)										
Guinea	2014–15	Outbreak	2	7	6	0	2.4–3.0	42	2.7 yrs	Dec 26, 2015
Laos	2015–16	Outbreak	1	11	25	0	2.3–3.9	88	3.5 yrs	Jan 11, 2016
Madagascar	2014–15	Outbreak	1	10	11	0	2.3–3.3	73	3 yrs	Sep 2, 2015
Burma (Myanmar)	2015	Outbreak	2	2	0	0	1.4–1.7	76	1.5 yrs	Oct 5, 2015
Nigeria	2005–15	Outbreak	2	0	0	1	7.3	72	6.6 yrs	Mar 4, 2015
Nigeria	2014–15	Outbreak	2	1	0	1	1.4	72	~1 yr	May 28, 2015
Nigeria	2013–16	Outbreak – importation	2	0	0	1	3.5	72	~3 yrs	Mar 23, 2016
Pakistan	2012–15	Outbreak	2	2	0	15	0.7–2.1	72	~2 yrs	Mar 28, 2015
Ukraine	2015	Outbreak	1	2	0	0	2.2–2.9	74	2.6 yrs	Jul 12, 2015
Immunodeficiency-associated VDPVs (iVDPVs)										
Algeria	2015	AFP patient	2	1	0	0	1.7	95	1.5 yrs	Jul 22, 2015
China	2015	AFP patient	2	1	0	0	0.8	99	<1 yr	Mar 12, 2015
China	2015	AFP patient	2	1	0	0	2.4	99	~2 yrs	Mar 19, 2015
Egypt	2015	AFP patient PID	2	1	0	0	1.9	94	1.7 yrs	Dec 9, 2015
Egypt	2016	Non-AFP PID	2	0	0	1	1.3	94	~1 yr	Apr 18, 2016
Egypt	2016	Non-AFP PID	2	0	0	1	2.0	94	<2 yrs	May 22, 2016
Nigeria	2015	AFP patient	2	1	0	0	0.7	72	<1 yr	Oct 9, 2015
India	2015	AFP patient CVID	2	1	0	0	2.7–4.0	82	2.3 yrs–4 yrs	Mar 8, 2016
India	2015	AFP patient XLA	2	1	0	0	0.7	82	7 mos	Feb 29, 2016
India	2015	Non-AFP SCID	3	0	0	1	4.5–10.2	82	3.9 yrs; 6 yrs	May 30, 2016
Iran	2015	AFP patient SCID	2	1	0	0	0.8–1.6	99	~1.5 yrs	Feb 7, 2016
Iran	2015	Non-AFP SCID 1	2	0	0	1	1.3–1.8	99	~1.5 yrs	Feb 16, 2016
Iran	2015	Non-AFP SCID 2	2	0	0	1	0.7	99	<1 yr	Oct 14, 2015
Iran	2015	Non-AFP SCID 3	2	0	0	1	1.1	99	1 yr	Oct 14, 2015
Iran	2015	Non-AFP SCID 4	2	0	0	1	1.8–2.2	99	2 yrs	Feb 8, 2016
Iraq	2015	AFP patient PID	2	1	2	0	1.9	76	1.7 yrs	Jul 23, 2015
Iraq	2016	AFP patient PID	2	1	0	0	0.8	76	<1 yr	Feb 13, 2016
Oman	2015	Non-AFP PID	2	0	0	1	0.8–1.6	99	~1.5 yrs	Nov 30, 2015
Turkey	2015	Non-AFP PID	3	0	0	1	1.7	96	1.5 yrs	Feb 22, 2015
Turkey	2015	AFP patient PID	2	1	0	0	0.7–0.8	96	<1 yr	Mar 20, 2015
UK	2015	Non-AFP PID	2	0	0	1	16.6–16.7	96	>29 yrs	Nov 17, 2015
West Bank and Gaza Strip	2015	Non-AFP SCID	2	0	0	1	1.0–1.9	96	1.7 yrs	May 3, 2016
Ambiguous VDPVs (aVDPVs)										
Algeria	2015	AFP patient	3	1	0	0	1.6	95	~1.5 yrs	May 5, 2015
Chad	2015	AFP patient	2	1	0	0	0.8	54	<1 yr	Jan 15, 2015
China	2015	Non-AFP	1	0	0	1	1.1	99	1 yr	Mar 20, 2015
Democratic Republic of the Congo	2015–16	AFP patient	2	4	0	0	0.7–1.8	79	1.5 yrs	Mar 29, 2016
Egypt	2015–16	Environmental sample	2	0	0	4	0.7–0.9	94	<1 yr	Mar 15, 2015
Ethiopia	2015	AFP patient	2	1	0	0	0.8	75	<1 yr	Mar 11, 2015
India	2015	AFP patient	2	1	0	0	0.8	82	<1 yr	Mar 8, 2015
India	2015	Environmental sample	2	0	0	15	0.7–1.4	82	7 mos–1.3 yrs	May 16, 2016
Iraq	2015	AFP patient	2	1	0	0	1.0–1.3	76	~1 yr	Nov 24, 2015
Kenya	2015	Environmental sample	2	0	0	1	0.8	81	<1 yr	Dec 30, 2015
Madagascar	2015	AFP patient	1	1	1	0	3.5–3.9	73	3.5 yrs	Feb 22, 2015
Netherlands	2015	Non-AFP	3	0	0	1	1.7	96	1.5 yrs	Jun 16, 2015
Niger	2015	Environmental sample	2	0	0	1	0.9	67	<1 yr	Dec 29, 2015

See table footnotes on next page.

TABLE. (Continued) Number of vaccine-derived polioviruses (VDPVs) detected, by classification and other selected characteristics — worldwide, January 2015–May 2016

Country	Year(s) detected*	Source†	Serotype	No. of isolates [§] January 2015–May 2016			VP1 divergence from Sabin OPV strain (%) [¶]	Routine OPV3 coverage (%)**	Estimated duration of VDPV replication ^{††}	Current status (date of last outbreak case, patient isolate, or environmental sample)
				No. of cases	No. of contacts	No. of non-AFP sources				
Nigeria	2016	AFP patient	2	1	0	0	0.9	72	<1 yr	May 18, 2016
Nigeria	2015	Environmental sample	2	0	0	4 ^{§§}	0.7–0.8	72	<1 yr	Mar 9, 2015
Pakistan	2015	AFP patient	2	2	0	0	1.0–1.2	72	~1 yr	Aug 20, 2015
Pakistan	2015	Environmental sample	2	0	0	8	0.7–1.0	72	~1 yr	Dec 12, 2015
Russia	2015	Environmental sample	2	0	0	1	17.6	97	>15 yrs	Sep 17, 2015
Republic of South Sudan	2015	AFP patient	2	1	0	0	1.6	44	~1.5 yrs	Apr 22, 2015
Senegal	2015	Environmental sample	2	0	0	1	0.7	85	<1 yr	Nov 5, 2015
Syria	2015	AFP patient	2	1	0	0	0.7	52	<1 yr	May 13, 2016
Turkey	2015	AFP contact	2	0	1	0	0.7	96	<1 yr	Jan 20, 2015

Abbreviations: AFP = acute flaccid paralysis; OPV = oral poliovirus vaccine; PID = primary immunodeficiency; SCID = severe combined immunodeficiency; XLA = X-linked agammaglobulinemia.

* Total years detected and cumulative totals for previously reported cVDPV outbreaks (Nigeria, Pakistan).

† Outbreaks list total cases clearly associated with cVDPVs. Some VDPV case isolates from outbreak periods might be listed as aVDPVs.

§ Total cases for VDPV-positive specimens from AFP cases and total VDPV-positive samples for environmental (sewage) samples.

¶ Percentage of divergence is estimated from the number of nucleotide differences in the VP1 region from the corresponding parental OPV strain.

** Coverage with 3 doses of oral poliovirus vaccine, based on 2014 data from the World Health Organization (WHO) Vaccine Preventable Diseases Monitoring System (2015 global summary) and WHO-UNICEF coverage estimates. National data might not reflect weaknesses at subnational levels. http://www.who.int/immunization/monitoring_surveillance/en/.

†† Duration of cVDPV circulation was estimated from extent of VP1 nucleotide divergence from the corresponding Sabin OPV strain; duration of immunodeficiency-associated VDPV replication was estimated from clinical record by assuming that exposure was from initial receipt of OPV; duration of ambiguous VDPV replication was estimated from sequence data.

§§ Three genetically linked isolates were classified as aVDPVs according to the VDPV guidelines (http://www.polioeradication.org/Portals/0/Document/Resources/VDPV_ReportingClassification.pdf), which require detection for >2 months.

Pakistan. Among the five independent cVDPV2 emergences reported previously (4), only one persisted during January 2015–May 2016, detected in 14 environmental samples collected in Sindh and one in Baluchistan. Two AFP cases reported in Federally Administered Tribal Areas and Khyber Pakhtunkhwa with onset in February 2015 were genetically linked to a new cVDPV2 emergence (0.7% divergent from parental Sabin 2). This new cVDPV2 emergence was not detected after February 2015. No cVDPVs have been detected in 2016.

Ukraine. In 2015, two genetically linked cVDPV1s (2.2%–2.9% VP1 divergence) were detected in southwestern Ukraine, from two AFP cases with onset dates of June 30 and July 7.

Detection of iVDPVs

After implementation of intensified surveillance for iVDPVs, detection of new iVDPV infections increased from eight in 2014 to 21 during January 2015–May 2016. (Table). During this reporting period, with the exception of two type 3 iVDPVs, all were type 2. Like cVDPVs, the cumulative serotype distribution since OPV introduction shows that type 2 iVDPVs are the most prevalent (66%), followed by type 1

(14%), type 3 (14%), and heterotypic mixtures (6%). Selected iVDPVs from the reporting period are described below.

Egypt. A male child aged 11 months with PID developed paralysis in December 2015; iVDPV2 was detected. In April 2016, an unrelated iVDPV2 was isolated from a nonparalyzed PID patient.

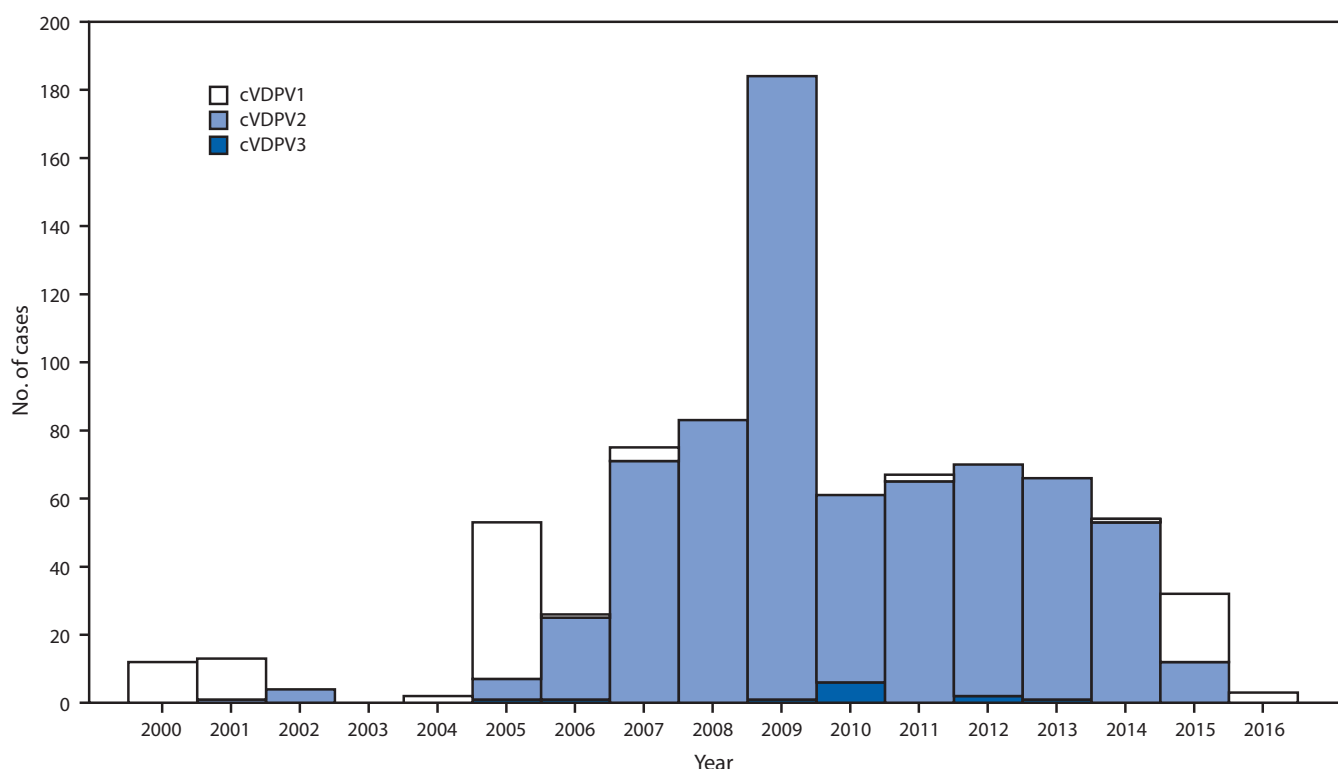
Iran. During this reporting period, five patients (one with AFP) were found to be excreting iVDPVs. A girl aged 6 months with severe combined immunodeficiency (SCID), who received OPV in March 2015, developed AFP in September 2015. The last positive sample from this child was in February 2016. Four nonparalytic SCID patients were found to be excreting type 2 iVDPVs; two of these patients (one each from Tehran and Ardebil provinces) died; the other two were from Golestan and Kermanshah provinces.

Iraq. A girl with PID developed AFP at age 8 months. In July 2015, iVDPV2 was detected, and the girl subsequently died.

Oman. A boy with major histocompatibility complex class II deficiency was found to be infected with iVDPV2 at age 9 months.

West Bank and Gaza. In October 2015, a girl aged 5 months with SCID who had not developed AFP was found to be infected with an iVDPV2. She remains hospitalized after bone marrow transplantation and continues to excrete iVDPV2.

FIGURE 2. Number of circulating vaccine-derived poliovirus (cVDPV) cases detected, by serotype — worldwide, January 2000–May 2016*



* Data through May 2016 as available by July 14, 2016.

Detection of aVDPVs

During January 2015–May 2016, aVDPVs were isolated in 19 countries (Table). The most divergent aVDPV (3.9% VP1 divergence) was isolated from an AFP case in Madagascar. This represented an emergence independent from a cVDPV emergence that circulated broadly in Madagascar during the same period. Report of aVDPVs in settings with immunization coverage <60% might indicate a risk for cVDPV emergence and further spread and potential gaps in surveillance. Selected aVDPVs from the reporting period are described below.

Chad. An aVDPV2 (0.8% VP1 divergence) was isolated from an AFP case with paralysis onset in January 2015 in Mayo-Kebbi Est Province.

Democratic Republic of the Congo. Four independent aVDPV2s were isolated from four AFP clinical samples: two in 2015 (0.8%–1.1% VP1 divergence) and two in 2016 (0.7%–1.7% VP1 divergence). The latest isolate from 2016 resembles an iVDPV2, but because no immunodeficient source patient has been identified, classification of this VDPV is pending.

Egypt. Four environmental samples contained aVDPVs (0.7%–0.9% VP1 divergence), three in 2015 and one in 2016. They were collected from four distinct collection sites during February 2015–March 2016.

Kenya. An aVDPV2 (0.8% VP1 divergence) was isolated from a sewage specimen collected in Nairobi in December 2015. The virus had four amino acid differences from Sabin 2, all in the neutralizing antigenic sites, suggesting an iVDPV. However, no immunodeficient source patient has been identified.

Madagascar. An aVDPV1 (3.9% VP1 divergence) was isolated from a patient in Nosy-Varika, Fianarantsoa Province, on the central east coast, who had AFP onset on January 31, 2015. Despite a small number of VP1 substitutions shared with the 2014 cVDPV1 isolates from Analalava, on the northwest coast, the sequence properties of this aVDPV1 are consistent with an independent VDPV1 emergence. Thus, two emergences of VDPV were detected, but only one sustained circulation.

Netherlands. An aVDPV3 was isolated from a non-AFP case in a Syrian refugee who arrived in Netherlands in 2014. The date of the last positive specimen (1.7% VP1 divergence) was June 16, 2015.

Nigeria. Four aVDPV2s (all from sewage samples; all with 0.7%–0.8% VP1 divergence) were isolated in Sokoto State during the reporting period; the most recent sample was collected on March 9, 2015. Three of the isolates were genetically linked, although closely related (within 2 nucleotide differences), and detection was limited to two serial collections, on February 9

and March 9. An aVDPV2 was isolated from an AFP patient who developed paralysis on May 14, 2016, in Jigawa State.

Pakistan. Ten aVDPV2s (two from AFP patients and eight from sewage samples; 0.7%–1.2% VP1 divergence) were isolated in 2015. The most recent aVDPV2 isolates were from an AFP patient in Sindh province in August 2015 (1.0% VP1 divergence), and from a sewage sample collected in Baluchistan in December 2015 (0.7% VP1 divergence).

Discussion

The number of cVDPV outbreaks worldwide increased since the January 2014–March 2015 reporting period; however, the intensity and number of AFP cases in cVDPV outbreaks declined. Inclusion of more tOPV rounds in the steadily improving supplementary immunization activities (SIAs)* and increased access to unimmunized children were important factors for interruption of cVDPV2 outbreaks in Afghanistan and South Sudan and for control of cVDPV2 outbreaks in Nigeria and Pakistan. The new outbreaks in Burma, Guinea, Laos, Madagascar, and Ukraine highlight the importance of maintaining high population immunity to all polioviruses, as well as sensitive AFP surveillance.

The expansion of environmental surveillance in countries at high risk has increased the sensitivity of poliovirus detection. However, detection of polioviruses from sewage presents logistical and technical challenges (4), including determination of VDPV genetic signatures (7). Determination of epidemiologic linkages from sequence data in environmental isolates represents an additional challenge. For example, highly divergent isolates, most likely representing iVDPVs based on the genetic signature, are classified as aVDPVs because of the absence of epidemiologic linkage to a known immunodeficient patient who is a chronic poliovirus excretor.

The frequency of cVDPV2 detection declined during January 2015–May 2016. However, the emergence of cVDPV2 in countries with low routine vaccination coverage underscores the risks from widening immunization gaps to type 2 polioviruses. The April 29, 2016, report of detection of a cVDPV2 isolate from sewage in Nigeria with 3.5% VP1 divergence suggests that gaps in surveillance had missed virus circulation. In response to this outbreak, three rounds of SIAs with monovalent oral poliovirus vaccine type 2 (mOPV2) were used in accessible areas of Borno State and neighboring districts in two other states (10). Detection of aVDPV2 isolates in environmental samples in Kenya and Egypt with six or seven VP1 nucleotide differences (<1 year of replication/circulation) did

* Supplementary immunization activities are mass vaccination campaigns conducted over a short period (days to weeks) during which a dose of OPV is administered to all children aged <5 years, regardless of previous vaccination history. Campaigns can be conducted nationally or in selected areas of a country.

Summary

What is already known about this topic?

Vaccine-derived polioviruses (VDPVs), genetically divergent strains from the oral poliovirus vaccine (OPV), fall into three classifications: 1) circulating VDPVs (cVDPVs) from outbreaks, 2) immunodeficiency-associated VDPVs (iVDPVs) from patients with primary immunodeficiencies, and 3) ambiguous VDPVs (aVDPVs) that cannot be more definitively identified. cVDPVs emerge in settings of low population immunity, can cause paralysis, and can sustain long-term circulation. Because >94% of cVDPVs isolated since 2006 and 66% of iVDPVs identified since OPV introduction are type 2, and because wild polio virus type 2 was declared eradicated in 2015, the World Health Organization coordinated worldwide replacement of trivalent OPV with bivalent OPV (types 1 and 3) in April 2016.

What is added by this report?

During January 2015–May 2016, new cVDPV outbreaks were identified in Burma, Guinea, Laos, Madagascar, and Ukraine, while cVDPV2 circulation in Nigeria and Pakistan sharply declined. Twenty-one newly identified persons in 10 countries were found to excrete iVDPVs.

What are the implications for public health practice?

The ultimate goal of the Global Polio Eradication Initiative is the cessation of all poliovirus circulation. The risk for iVDPV emergence will continue as long as OPV is used. The switch from trivalent OPV to bivalent OPV in April 2016 was the first step to phasing out the use of all OPV, setting the stage for a total worldwide shift from OPV to IPV.

not lead to a recommendation for use of mOPV2; scope of response is based on risk of spread and the estimated duration of circulation before detection.

WPV2, which has not been detected since 1999, was declared globally eradicated on September 20, 2015, and WPV3 has not been detected worldwide since 2012. A key goal of the polio endgame strategic plan (6) is the global cessation of all OPV use, starting with OPV2, which will ultimately eliminate the risk for cVDPV outbreaks and new iVDPV infections. During a 2-week period in April 2016, the Global Polio Eradication Initiative coordinated worldwide withdrawal of tOPV (types 1, 2, and 3) and replacement with bOPV (types 1 and 3), which was accomplished by May 2016 in 150 countries and territories that used any OPV in childhood vaccination schedules. The Global Polio Eradication Initiative and Global Polio Laboratory Network have continued to strengthen AFP and poliovirus surveillance during 2016. Routine immunization services also are being strengthened, and most countries incorporated at least 1 dose of IPV into routine childhood immunization schedules in 2015 (6). This was limited from the planned introduction in all 126 countries that used OPV exclusively for routine immunization because of a global IPV supply shortage. To reduce the risk for iVDPV spread from

long-term chronic excretors, maintenance of high levels of routine vaccination coverage will be necessary during the polio endgame.

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Contents

- 421 Cessation of use of trivalent oral polio vaccine and introduction of inactivated poliovirus vaccine worldwide, 2016
- 427 Performance of acute flaccid paralysis (AFP) surveillance and incidence of poliomyelitis, 2016

Sommaire

- 421 Abandon du vaccin antipoliomyélique oral trivalent et introduction du vaccin antipoliomyélique inactivé à l'échelle mondiale, 2016
- 427 Fonctionnement de la surveillance de la paralysie flasque aiguë (PFA) et incidence de la poliomyélite, 2016

Cessation of use of trivalent oral polio vaccine and introduction of inactivated poliovirus vaccine worldwide, 2016

Lee M. Hampton,^a Margaret Farrell,^b Alejandro Ramirez-Gonzalez,^c Lisa Menning,^c Stephanie Shendale,^c Ian Lewis,^d Jennifer Rubin,^d Julie Garon,^e Jennifer Harris,^a Terri Hyde,^a Steven Wassilak,^a Manish Patel,^f Robin Nandy,^b and Diana Chang-Blanc,^c on behalf of the Immunization Systems Management Group of the Global Polio Eradication Initiative

Introduction

Since the 1988 World Health Assembly resolution to eradicate poliomyelitis, transmission of the 3 types of wild poliovirus (WPV) has been greatly reduced.¹ WPV type 2 (WPV2) has not been detected since 1999 and was declared eradicated in September 2015. Given that WPV type 3 has not been detected since November 2012, WPV type 1 (WPV1) is likely to be the sole WPV remaining in circulation. This marked progress has been achieved through widespread use of oral poliovirus vaccines (OPVs), most commonly trivalent OPV (tOPV), which contains types 1, 2 and 3 live, attenuated polioviruses, and has been a mainstay of efforts to prevent polio since the early 1960s. Attenuated polioviruses in OPV can undergo genetic changes during replication, and in communities with low vaccination coverage rarely result in vaccine-derived polioviruses (VDPVs) that can cause paralytic polio indistinguishable from the disease caused by WPVs.²

Among the 721 polio cases caused by circulating VDPVs (cVDPVs) detected between January 2006 and May 2016,

Abandon du vaccin antipoliomyélique oral trivalent et introduction du vaccin antipoliomyélique inactivé à l'échelle mondiale, 2016

Lee M. Hampton,^a Margaret Farrell,^b Alejandro Ramirez-Gonzalez,^c Lisa Menning,^c Stephanie Shendale,^c Ian Lewis,^d Jennifer Rubin,^d Julie Garon,^e Jennifer Harris,^a Terri Hyde,^a Steven Wassilak,^a Manish Patel,^f Robin Nandy,^b et Diana Chang-Blanc,^c au nom du Groupe de gestion des systèmes de vaccination de l'Initiative mondiale pour l'éradication de la poliomyélite

Introduction

Depuis la résolution de l'Assemblée mondiale de la Santé de 1988 d'éradiquer la poliomyélite, la transmission des 3 types de poliovirus sauvages (PVS) a considérablement régressé.¹ Le PVS de type 2 (PVS2) n'a pas été détecté depuis 1999 et a été déclaré éradiqué en septembre 2015. Le PVS de type 3 n'ayant pas été détecté depuis novembre 2012, il est probable que le seul PVS encore en circulation soit le PVS de type 1 (PVS1). Ces progrès remarquables ont été obtenus grâce à l'utilisation généralisée des vaccins antipoliomyéliques oraux (VPO), le plus souvent le VPO trivalent (VPOt) qui contient les poliovirus vivants atténués de type 1, 2 et 3 et qui a joué un rôle fondamental dans la prévention de la poliomyélite depuis le début des années 1960. Les poliovirus atténués contenus dans le VPO peuvent subir des modifications génétiques lors de la réplication; dans les communautés où la couverture vaccinale est insuffisante, ces modifications peuvent, même si cela demeure rare, générer des poliovirus dits dérivés d'une souche vaccinale (PVDV) susceptibles d'entraîner une poliomyélite paralytique qu'il est impossible de distinguer de la maladie causée par les PVS.²

Parmi les 721 cas de poliomyélite due aux PVDV circulants (PVDVc) recensés entre janvier 2006 et mai 2016, plus de 94% étaient

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¹ See No. 19, 2016, pp. 251–256.

² See No. 31, 2016, pp. 365–374.

¹ Voir N° 19, 2016, p. 251–256.

² Voir N° 31, 2016, p. 365–374.

type 2 cVDPVs (cVDPV2s) accounted for >94%.² Eliminating the risk of polio caused by VDPVs requires the stopping of all OPV use. The first stage of OPV withdrawal involved a global, synchronized cessation of tOPV use planned for 18 April–1 May 2016, replacing tOPV with bivalent OPV (bOPV) containing only types 1 and 3 polioviruses, and withdrawing OPV type 2 from all immunization activities.³ Complementing the switch from tOPV to bOPV was the introduction of at least one dose of injectable, trivalent inactivated poliovirus vaccine (IPV) into childhood immunization schedules which reduces the risks from, and facilitates responses to, cVDPV2 outbreaks. This report summarizes global progress in the cessation of tOPV use and the introduction of IPV.

All 155 countries and territories that were continuing use of OPV in immunization schedules in 2015 reported that they had ceased use of tOPV by mid-May 2016. As of 31 August 2016, 173 (89%) of 194 WHO Member States included IPV in their immunization schedules. The cessation of tOPV use is a significant step in completing the global effort to eradicate polio; however, careful surveillance for polioviruses and prompt, aggressive responses to outbreaks are still needed to create a world free from the disease.

Global cessation of use of trivalent OPV

Although the global cessation of tOPV use is essential for eliminating cVDPV2s, it carries some risks in facilitating the spread of undetected or newly emergent cVDPV2s among persons without immunity to type 2 poliovirus infections after the switch.^{4,5} To stop the spread of existing cVDPV2s before the switch and to reduce risks for post-switch outbreaks, population immunity to type 2 poliovirus at the time of the switch was boosted through implementation of at least 116 supplementary immunization activities (SIAs) with tOPV in 42 OPV-using countries during November 2015–April 2016. Afghanistan, Nigeria and Pakistan conducted SIAs with IPV in selected regions before ceasing tOPV use. In addition, the synchronized timing of the switch aimed to prevent exportations of type 2 polioviruses from areas continuing to use tOPV to neighbouring areas that had ceased tOPV use.^{3,4} All 155 countries and territories using OPV in 2015 reported cessation of use of tOPV by 12 May 2016 (*Map 1*).⁶ To facilitate the global cessation of tOPV use, all manufacturers of OPV ceased production of tOPV before the switch and after several years of communication and close coordination with the Global Polio Eradication Initiative (GPEI).

imputables aux PVDVc de type 2 (PVDVc2).² Pour éliminer le risque de poliomyélite causée par les PVDV, il sera nécessaire d'abandonner tous les VPO. La première étape du retrait des VPO a consisté à cesser d'utiliser le VPOt de manière synchronisée, à l'échelle mondiale, entre le 18 avril et le 1^{er} mai 2016, et à le remplacer par le VPO bivalent (VPOb) contenant uniquement les poliovirus de types 1 et 3, supprimant ainsi le VPO de type 2 de toutes les activités de vaccination.³ En complément du passage du VPOt au VPOb, l'introduction d'au moins une dose de vaccin antipoliomyélique inactivé (VPI) trivalent injectable dans le calendrier vaccinal pédiatrique permet de réduire les risques liés aux flambées de poliomyélite due au PVDVc2 et de faciliter la riposte à ces flambées. Ce rapport récapitule les progrès accomplis à l'échelle mondiale dans l'abandon du VPOt et l'introduction du VPI.

Les 155 pays et territoires qui utilisaient encore le VPO dans le calendrier vaccinal en 2015 ont indiqué avoir cessé d'utiliser le VPOt à la mi-mai 2016. Au 31 août 2016, 173 (89%) des 194 États Membres de l'OMS avaient introduit le VPI dans le calendrier vaccinal. L'abandon du VPOt est une étape importante vers l'éradication de la poliomyélite dans le monde, mais il demeure nécessaire de surveiller attentivement les poliovirus et de riposter rapidement et énergiquement aux flambées de poliomyélite afin de parvenir à un monde exempt de poliomyélite.

Abandon du VPO trivalent à l'échelle mondiale

Bien qu'il soit essentiel de cesser d'utiliser le VPOt dans le monde pour éliminer les PVDVc2, cette mesure comporte le risque de faciliter la propagation de PVDVc2 non détectés ou émergents chez les personnes non immunisées contre les infections à poliovirus de type 2 après la transition du VPOt au VPOb.^{4,5} Pour mettre fin à la propagation des PVDVc2 existants avant la transition et pour réduire les risques de flambées épidémiques après la transition, l'immunité de la population contre les poliovirus de type 2 au moment de la transition a été renforcée en menant 116 activités de vaccination supplémentaire (AVS) avec le VPOt dans 42 pays utilisant le VPO entre novembre 2015 et avril 2016. L'Afghanistan, le Nigéria et le Pakistan ont également mené des AVS avec le VPI dans certaines régions avant de cesser d'utiliser le VPOt. En outre, la synchronisation du passage du VPOt au VPOb visait à prévenir l'exportation de poliovirus de type 2 des régions qui continuaient à utiliser le VPOt vers les régions voisines qui avaient abandonné le VPOt.^{3,4} Les 155 pays et territoires qui utilisaient le VPO en 2015 ont indiqué avoir cessé d'utiliser le VPOt au 12 mai 2016 (*Carte 1*).⁶ Pour faciliter l'abandon du VPOt à l'échelle mondiale, tous les fabricants de VPO ont cessé la production de VPOt avant la transition, après plusieurs années de communication et de coordination étroite avec l'Initiative mondiale pour l'éradication de la poliomyélite (IMEP).

³ Global Polio Eradication Initiative. Polio eradication and endgame strategic plan 2013–2018. Geneva, Switzerland: World Health Organization; 2013. Available at: http://www.polioeradication.org/Portals/0/Document/Resources/StrategyWork/PEESP_EN_US.pdf; accessed August 2016.

⁴ Duintjer Tebbens RJ, Hampton LM, Thompson KM. Implementation of coordinated global serotype 2 oral poliovirus vaccine cessation: risks of potential non-synchronous cessation. *BMC Infect Dis.* 26 May;16(1):231.

⁵ Duintjer Tebbens RJ, Hampton LM, Thompson KM. Implementation of coordinated global serotype 2 oral poliovirus vaccine cessation: risks of inadvertent trivalent oral poliovirus vaccine use. *BMC Infect Dis.* 1 June 2016;16(1):237.

⁶ Five countries ceased all regular use of any OPV between early 2015 and March 2016. The remaining 150 countries continuing use of OPV in April 2016 ceased all use of tOPV by 12 May 2016.

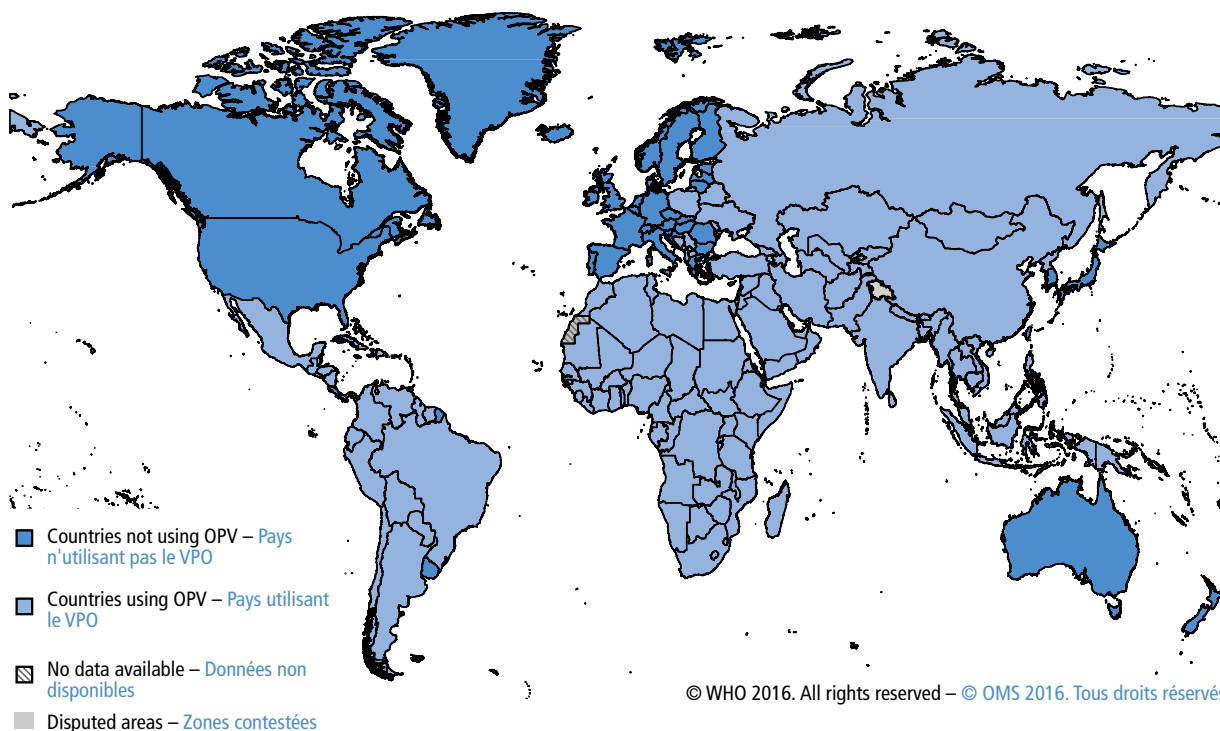
² Initiative mondiale pour l'éradication de la poliomyélite. Plan stratégique pour l'éradication de la poliomyélite et la phase finale 2013–2018. Genève (Suisse): Organisation mondiale de la Santé; 2013. Disponible à l'adresse http://www.polioeradication.org/Portals/0/Document/Resources/StrategyWork/PEESP_FR_A4.pdf; consulté le 14 août 2016.

⁴ Duintjer Tebbens RJ, Hampton LM, Thompson KM. Implementation of coordinated global serotype 2 oral polio-virus vaccine cessation: risks of potential non-synchronous cessation. *BMC Infect Dis.* 26 May;16(1):231.

⁵ Duintjer Tebbens RJ, Hampton LM, Thompson KM. Implementation of coordinated global serotype 2 oral polio-virus vaccine cessation: risks of inadvertent trivalent oral poliovirus vaccine use. *BMC Infect Dis.* 1 June 2016;16(1):237.

⁶ Cinq pays ont cessé l'utilisation courante de tous les VPO entre début 2015 et mars 2016. Les 150 autres pays qui utilisaient toujours le VPO en avril 2016 avaient totalement cessé d'utiliser le VPOt au 12 mai 2016.

Map 1 **Countries using oral poliovirus vaccine (OPV) in 2015**
 Carte 1 **Pays qui utilisaient le vaccin antipoliomyélitique oral (VPO) en 2015**



To reduce the risk of inadvertent or intentional use of tOPV after the switch, which could lead to the emergence of new cVDPV2s,⁵ a combination of external and in-country monitors visited over 160 000 vaccine stores and service delivery points in participating countries and territories. The monitors verified the absence of tOPV from each country's vaccine supply cold chain. Their findings were reviewed by a validation committee, whose assessment of whether or not tOPV had been removed from the cold chain was provided to the national government and later to WHO. By 31 August 2016, all countries and territories (with the exception of 2) that had used OPV in 2015 had submitted validation reports to WHO.

Type 2 poliovirus strains held in research or manufacturing facilities could also cause polio outbreaks if released into a population. To prevent such outbreaks, countries should ensure that all remaining type 2 polioviruses, including WPV2s, VDPV2s, and the type 2 Sabin polioviruses used in tOPV and monovalent OPV type 2 (mOPV2), are destroyed or appropriately contained in certified poliovirus-essential facilities in accordance with the third *Global Action Plan to minimize poliovirus facility-associated risk* (GAPIII).^{3,7} Should an outbreak of type 2 poliovirus occur, GPEI has developed a response protocol and assembled a global stockpile of mOPV2 managed by UNICEF and stored under containment conditions, to be released on the instruction of

Pour réduire le risque d'utilisation accidentelle ou intentionnelle de VPOt après la transition, ce qui pourrait conduire à l'émergence de nouveaux PVDVc2,⁵ des contrôleurs extérieurs et nationaux ont visité plus de 160 000 lieux de stockage de vaccins et de prestation de services dans les pays et territoires participant à la transition. Les contrôleurs ont vérifié l'absence de VPOt dans la chaîne du froid de l'approvisionnement en vaccins de chaque pays. Les résultats des contrôles dans chaque pays et territoire ont été examinés par un comité de validation dont l'évaluation sur le retrait ou non du VPOt de la chaîne du froid a été transmise au gouvernement national, puis à l'OMS. Au 31 août 2016, tous les pays et territoires qui utilisaient le VPO en 2015, sauf 2, avaient remis un rapport de validation à l'OMS.

Les souches de poliovirus de type 2 détenues dans les structures de recherche ou les sites de production peuvent aussi donner lieu à des flambées de poliomyélite si elles sont libérées dans la population. Pour prévenir ces flambées, les pays doivent s'assurer que tous les poliovirus de type 2 restants, notamment les PVS2, les PVDV2 et les poliovirus Sabin de type 2 utilisés dans les VPOt et les VPO monovalents de type 2 (VPOm2), sont détruits ou correctement confinés dans des établissements certifiés pour la conservation des poliovirus essentiels, conformément au troisième *Plan d'action mondial de l'OMS visant à réduire au minimum le risque associé aux établissements* (GAPIII).^{3,7} Dans le cas où des flambées épidémiques dues aux poliovirus de type 2 surviendraient, l'IMEP a élaboré un protocole de riposte et constitué un stock mondial de VPOm2, géré

⁷ See No. 32, 2015, pp. 396–408.

⁷ Voir N° 32, 2015, p. 396–408.

the WHO Director-General. As of 31 August 2016, this stockpile contains 36 million mOPV2 doses in finished vials. An additional 50 million mOPV2 doses will become available between September and December 2016, and a further 50 million doses by March 2017. Hundreds of millions of doses stored in bulk form are available for conversion into finished mOPV2 doses. GPEI has also created an IPV stockpile for use in outbreak responses. Surveillance of acute flaccid paralysis cases is supplemented by environmental surveillance of polioviruses in sewage in at least 36 countries to help identify and respond to the spread of type 2 polioviruses in those countries.⁸

Global introduction of inactivated poliovirus vaccine

To further reduce the risks of type 2 poliovirus outbreaks after the cessation of tOPV use, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization recommended in 2012 that the immunization schedules of all countries include at least one dose of IPV.³ IPV protects against paralytic polio from type 2 polioviruses and can facilitate interruption of transmission during cVDPV2 outbreaks by enhancing immunologic response to mOPV2 and reducing the duration and amount of viral shedding. In addition, IPV aids in eradicating WPV by boosting immunity to types 1 and 3 polioviruses in individuals who have received bOPV or tOPV.

Efforts to introduce IPV to the 126 countries using only OPV at the beginning of 2013 have been impacted by the challenges manufacturers of IPV have encountered in scaling up production to meet increased demand. This is in addition to the increased need for IPV in SIAs targeting WPV1 in polio endemic countries and the need to stockpile IPV for outbreak response. As of 31 August 2016, 105 of the 126 countries using only OPV at the beginning of 2013 had introduced IPV, resulting in 173 (89%) of 194 WHO Member States using IPV. However, 20 countries have had to delay introduction of IPV until adequate supplies become available which is not likely before the fourth quarter of 2017 (*Map 2*). In addition, 29 countries that previously introduced IPV are expected to run out of IPV nationwide before they receive their next supply of IPV in late 2017, and Cabo Verde has opted to postpone its introduction until 2017 to avoid a similar stock-out.⁹

In response to the shortage of IPV, GPEI has prioritized allocating the limited IPV supply first to Afghanistan, Nigeria, and Pakistan because of endemic WPV transmission; second to the other 33 countries considered at highest risk of cVDPV2 outbreaks; third to SIAs conducted in response to polio outbreaks; and finally to countries considered at low risk of polio outbreaks. Countries considered at high risk of cVDPV2 outbreaks¹⁰

par l'UNICEF et conservé dans des conditions de confinement, qui peut être mis à disposition sur instruction du Directeur général de l'OMS. Au 31 août 2016, ce stock contenait 36 millions de doses de VPOM2 en flacons finis. Cinquante millions de doses supplémentaires de VPOM2 deviendront disponibles entre septembre et décembre 2016, et 50 autres millions d'ici mars 2017. Des centaines de millions de doses stockées en vrac sont disponibles pour être conditionnées en doses finies de VPOM2. L'IMEP a également constitué un stock de VPI à utiliser en cas de flambées épidémiques. La surveillance des cas de paralysie flasque aiguë s'accompagne d'une surveillance environnementale visant à détecter les poliovirus dans les eaux usées dans au moins 36 pays afin d'aider à identifier et à riposter à la propagation de poliovirus de type 2 dans ces pays.⁸

Introduction mondiale du vaccin antipoliomyélitique inactivé

Pour réduire encore davantage les risques de flambées épidémiques dues aux poliovirus de type 2 après l'abandon du VPOT, le Groupe stratégique consultatif d'experts (SAGE) sur la vaccination de l'OMS a recommandé en 2012 que les calendriers vaccinaux de tous les pays comportent au moins une dose de VPI.³ Le VPI protège de la poliomyélite paralytique due aux poliovirus de type 2, il pourrait faciliter l'interruption de la transmission lors de flambées dues aux PVDVc2 en renforçant la réaction immunitaire au VPOM2 et en réduisant la durée d'élimination du virus et sa quantité, et contribuer à l'éradication du PVS en renforçant l'immunité contre les poliovirus de types 1 et 3 chez les personnes qui ont reçu le VPOT ou le VPOT.

Les efforts pour introduire le VPI dans les 126 pays qui utilisaient uniquement le VPO début 2013 se sont heurtés aux difficultés des fabricants à augmenter la production afin de répondre à la demande croissante de VPI et aux quantités accrues de VPI nécessaires pour les AVS visant le PVS1 dans les pays d'endémie de poliomyélite, et à la nécessité de stocker des VPI pour la riposte aux flambées épidémiques. Au 31 août 2016, 105 des 126 pays qui utilisaient uniquement le VPO début 2013 avaient introduit le VPI, portant à 173 sur 194 (89%) le nombre d'États Membres de l'OMS qui utilisent le VPI. Néanmoins, 20 pays ont dû retarder l'introduction du VPI jusqu'à ce qu'un approvisionnement suffisant en VPI soit disponible, ce qui n'arrivera vraisemblablement pas avant le dernier trimestre 2017 (*Carte 2*). En outre, selon les prévisions, 29 pays qui ont déjà introduit le VPI auront épuisé leurs stocks nationaux avant de recevoir le prochain approvisionnement fin 2017 et Cabo Verde a préféré retarder l'introduction du VPI jusqu'en 2017 afin d'éviter une rupture de stock similaire.⁹

Face à cette pénurie de VPI, l'IMEP a décidé d'allouer prioritairement les stocks limités de VPI d'abord à l'Afghanistan, au Nigeria et au Pakistan touchés par une transmission endémique de PVS, puis aux 33 autres pays considérés à haut risque de flambées épidémiques dues aux PVDVc2, ensuite aux AVS menées en réponse aux flambées de poliomyélite, et enfin aux pays considérés à faible risque de flambées de poliomyélite. Certains pays considérés à haut risque de flambées dues aux PVDVc2¹⁰ utilisent

⁸ See No. 15, 2016, pp. 193–202.

⁹ Of these countries, 8 are Pacific Island countries.

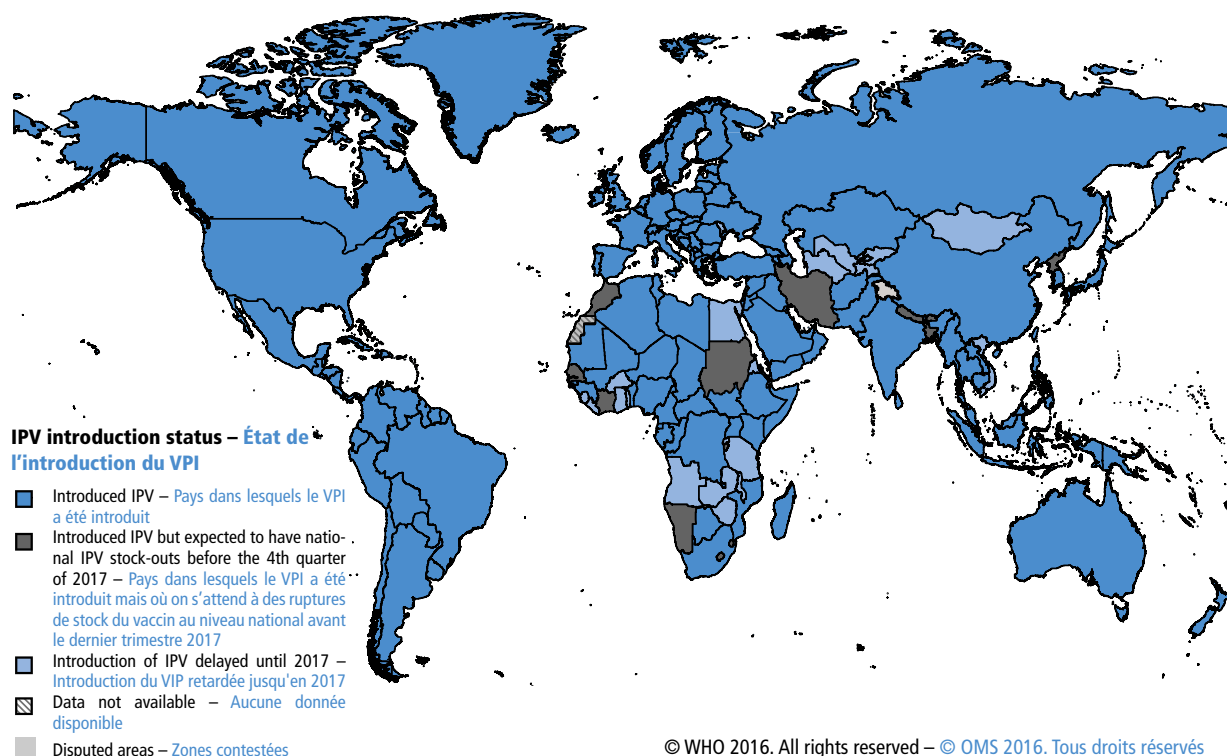
¹⁰ Countries are considered to be a high risk for a cVDPV2 outbreak if they have experienced a cVDPV outbreak since 2000, or an endemic WPV transmission, or an estimated routine immunization coverage of <80% for the third dose of a vaccine containing diphtheria, tetanus and pertussis antigens.

⁸ Voir N° 15, 2016, p. 193–202.

⁹ Parmi ces pays, 8 sont des pays insulaires du Pacifique.

¹⁰ Les pays sont considérés à haut risque de flambées dues aux PVDVc2 s'ils ont été touchés par une épidémie de poliomyélite à PVDVc2 depuis 2000 ou par une transmission endémique de PVS, ou si leur couverture vaccinale systématique est inférieure à 80% pour la troisième dose d'un vaccin contenant les antigènes de la diphtérie, du tétanos et de la coqueluche.

Map 2 **Global status of introduction of inactivated poliovirus vaccine, by country (IPV), 31 August 2016**
 Carte 2 **Introduction du vaccin antipoliomyélique inactivé (VIP) dans le monde, situation par pays au 31 août 2016**



are either providing IPV to infants through routine immunization service delivery, or planning to introduce IPV by the end of 2016. To use limited supplies of IPV efficiently, SAGE has encouraged countries to consider administering 2 fractional doses of IPV intradermally to children eligible for IPV instead of a full intramuscular (IM) dose.¹¹ Two fractional doses of IPV elicit a stronger immune response than a single full IM dose of IPV, yet each fractional dose requires only one fifth the volume of a full IM dose. Sri Lanka and India have both begun administering 2 fractional doses of IPV to children through their routine immunization services.

Discussion

The synchronized global switch from tOPV to bOPV operated smoothly due to the cessation of tOPV use in all countries and territories by mid-May 2016. The 721 cases of polio caused by cVDPV2s during 2006–2016 indicate both why the switch was necessary and why multiple precautions were taken to prevent cVDPV2s from later emerging or spreading.² Maintaining strong surveillance and response systems that can detect polioviruses, and responding promptly and aggressively when detected, is essential to preserving and building on the gains achieved in polio eradication since 1988.

le VPI pour vacciner les nourrissons dans le cadre d'une vaccination systématique, d'autres prévoient d'introduire le VPI d'ici à la fin 2016. Pour utiliser efficacement les stocks limités de VPI, le SAGE a encouragé les pays à envisager l'administration de 2 doses fractionnées de VPI par voie intradermique aux enfants éligibles au VPI au lieu d'une dose complète par voie intramusculaire.¹¹ Deux doses fractionnées de VPI engendrent une meilleure réaction immunitaire qu'une seule dose complète par voie intramusculaire, alors que chacune d'elle ne nécessite qu'un cinquième du volume de la dose complète. Le Sri Lanka et l'Inde ont ainsi commencé l'administration de 2 doses fractionnées de VPI aux enfants dans le cadre de leurs services de vaccination systématique.

Discussion

La transition mondiale synchronisée du VPOT au VPOB s'est déroulée sans encombre puisque tous les pays et territoires avaient cessé d'utiliser le VPOT à la mi-mai 2016. Les 721 cas de poliomyélite due aux PVDVc2 entre 2006 et 2016 illustrent la raison pour laquelle la transition était nécessaire et les multiples précautions prises pour prévenir l'émergence ou la propagation ultérieures de PVDVc2.² Pour préserver les acquis et poursuivre la lutte contre la poliomyélite amorcée en 1988, il sera essentiel de maintenir une surveillance très attentive et des systèmes de riposte capables de détecter les poliovirus et d'agir rapidement et énergiquement le cas échéant. La détection

¹¹ See No. 21, 2016, pp. 266–284.

¹¹ Voir N° 21, 2016, p. 266-284.

The prompt detection and destruction either of tOPV vials found in the cold chain after the switch, or of mOPV2 vials found after completion of a mOPV2 SIA, will also help to prevent new cVDPV2s from emerging in the future. Ultimately, the success of the withdrawal of tOPV and associated activities, such as the tOPV and IPV SIAs held in the months before the switch and the global introduction of IPV, will be measured by the number of polio cases caused by cVDPV2s occurring after tOPV withdrawal, with fewer cases indicating greater success.

No new cVDPV outbreaks have been identified in 2016.² In April 2016, a cVDPV2 was identified in an environmental sample collected in March 2016, before cessation of tOPV use, in northeastern Nigeria; however, genetic testing indicated that it was part of a known cVDPV2 lineage that was undetected after isolation from an environmental sample in early 2014.¹² Following the protocol for responding to detection of type 2 poliovirus after the switch and utilizing the prepared mOPV2 stockpile, SIAs with mOPV2 were implemented in northeastern Nigeria after detection of the cVDPV2. An SIA with fractional dose IPV is planned for the same area later in September, and SIAs with mOPV2 are planned in October and November for the neighbouring countries of Cameroon, Chad and Niger. The response to the identification in August of 2 polio cases caused by WPV1 in northeastern Nigeria is expected to lead to further strengthening of surveillance as well as population immunization, through vaccination, in that area.¹³

As of 31 August 2016, new type 2 ambiguous vaccine derived polioviruses (aVDPV2s) – VDPV2s that cannot be classified as either circulating VDPV2s or immunodeficiency-related VDPV2s after adequate investigation – have been identified in the Democratic Republic of the Congo, Egypt, India, Kenya, Nigeria, Pakistan, Senegal, and the Syrian Arab Republic. However, these aVDPV2s have all had relatively few genetic changes. All of the affected countries conducted SIAs with tOPV in 2016 in preparation for the switch. Specifically in response to the detections of these aVDPV2s, a localized SIA with tOPV was held in early May in Egypt, a localized SIA with fractionally-dosed IPV was held in June in India, and a series of mOPV2 SIAs was conducted in Nigeria. In addition, a localized mOPV2 SIA is planned in Pakistan. As of 31 August 2016, additional VDPV2s had also been identified in Ukraine and Yemen and had not yet been classified as cVDPV2s, aVDPV2s, or iVDPV2s (immunodeficiency-associated vaccine-derived polioviruses) as they were under investigation.

The introduction of IPV into the immunization schedules of 104 countries since 2013 is a significant achievement despite the challenges imposed by the global

et la destruction rapides de tout flacon de VPOt encore présent dans la chaîne du froid après la transition, et de tout flacon de VPOM2 à l'issue d'une activité de vaccination supplémentaire utilisant le VPOM2, contribuera également à prévenir l'émergence de nouveaux PVDVc2 à l'avenir. À terme, le succès du retrait du VPOt et des activités associées, comme les AVS avec le VPOt et le VPI menées dans les mois qui ont précédé la transition et l'introduction mondiale du VPI, se mesurera par le nombre de cas de poliomyélite due aux PVDVc2 qui se déclareront après le retrait du VPOt; plus ce nombre sera faible, plus le succès sera grand.

Aucune nouvelle flambée épidémique due aux PVDVc n'avait été détectée en 2016.² En avril 2016, un PVDVc2 a été identifié dans un échantillon environnemental prélevé en mars 2016 dans le nord-est du Nigéria avant l'abandon du VPOt, mais les tests génétiques indiquent qu'il fait partie d'une lignée de PVDVc2 connue non détectée après isolement à partir d'un échantillon environnemental début 2014.¹² Conformément au protocole de riposte en cas de détection d'un poliovirus de type 2 après la transition et d'utilisation du stock de VPOM2 constitué, des AVS avec le VPOM2 ont été menées dans le nord-est du Nigéria après la détection du PVDVc2. Une activité de vaccination supplémentaire utilisant des doses fractionnées de VPI est prévue dans cette même région en septembre, et des AVS avec le VPOc2 sont planifiées en octobre et novembre dans les pays voisins (Cameroun, Niger et Tchad). La réaction attendue à l'identification en août de 2 cas de poliomyélite due au PVS1 dans le nord-est du Nigéria devrait conduire à renforcer la surveillance et, par la vaccination, l'immunité de la population contre les infections à poliovirus dans cette région.¹³

Au 31 août 2016, de nouveaux poliovirus dérivés d'une souche vaccinale de type 2 ambigu (PVDVa2), qui sont des PVDV2 que l'on ne peut pas classer comme PVDV2 circulants ou comme PVDV2 liés à l'immunodéficience après une investigation adéquate, avaient été identifiés en Égypte, en Inde, au Kenya, au Nigéria, au Pakistan, en République démocratique du Congo, au Sénégal et en Syrie. Néanmoins, ces PVDVa2 avaient tous subi relativement peu de modifications génétiques. Tous les pays touchés ont mené des activités de vaccination supplémentaire avec le VPOt en 2016 en prévision de la transition. Pour riposter spécifiquement à la détection de ces PVDVa2, une activité de vaccination supplémentaire localisée avec le VPOt a été menée début mai en Égypte, une activité de vaccination supplémentaire localisée utilisant des doses fractionnées de VPI a été conduite en juin en Inde, et une série d'AVS utilisant le VPO de type 2 monovalent ont été menées au Nigéria. Une activité de vaccination supplémentaire localisée avec le VPO de type 2 monovalent est également prévue au Pakistan. Au 31 août 2016, deux PVDV2 avaient également été détectés en Ukraine et au Yémen mais n'avaient pas encore été classifiés comme étant circulants (PVDVc2), ambigus (PVDVa2) ou associés à un déficit humanitaire (PVDVi2) car encore en cours d'identification.

L'introduction du VPI dans le calendrier vaccinal de 104 pays depuis 2013 est un accomplissement majeur nonobstant les difficultés liées à la pénurie mondiale. Un soutien extérieur

¹² See No. 31, 2016, pp. 375–380.

¹³ World Health Organization. Government of Nigeria reports 2 wild polio cases, first since July 2014. Available at: <http://www.who.int/mediacentre/news/releases/2016/nigeria-polio/en/>; accessed August 2016.

¹² Voir N° 31, 2016, p. 375–380.

¹³ Organisation mondiale de la Santé. Les autorités nigérianes notifient 2 cas d'infection par un poliovirus sauvage, les premiers depuis juillet 2014. Disponible à l'adresse <http://www.who.int/mediacentre/news/releases/2016/nigeria-polio/fr/>; consulté en août 2016.

supply shortage. Continued external support for IPV introduction in countries that have not yet been able to introduce IPV due to supply shortages, but planning to do so once shortages have been resolved, as well as the strengthening of routine immunization systems that distribute and administer IPV, will help to maximize the benefit of IPV for all children.

The experience of tOPV withdrawal will contribute to future success in the cessation of all OPV use, primarily the withdrawal of bOPV. The cooperation of all OPV using countries and territories in ending tOPV use in a synchronized manner was an unprecedented public health achievement. This synchronized withdrawal was accomplished through the essential work performed by immunization workers in the countries and territories that stopped use of tOPV, as well as the preparation and communications over two years of GPEI, its partner organizations, OPV manufacturers, and country and territorial governments. The active support of the senior leaders of GPEI and national ministries of health was critical, as was the cooperation of all OPV manufacturers in ceasing production and distribution of tOPV and ensuring the availability and timely delivery of bOPV. Combined with the eradication of WPV, the ultimate withdrawal of all OPV from use will help to create a world free from polio.

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continu pour l'introduction du VPI dans les pays qui n'ont pas encore pu l'introduire mais qui prévoient de le faire une fois que la pénurie sera terminée et le renforcement des systèmes de vaccination systématique qui distribuent et administrent le VPI aideront à maximiser les avantages du VPI pour tous les enfants.

L'expérience acquise à partir du retrait du VPOt contribuera au succès des prochaines étapes nécessaires pour l'abandon de tous les VPO, en commençant par le retrait du VPOb. La coopération de tous les pays et territoires utilisant le VPO pour abandonner le VPOt de manière synchronisée est un accomplissement de santé publique sans précédent. Ce retrait synchronisé est le fruit d'un travail essentiel réalisé par les agents chargés de la vaccination dans les pays et territoires qui ont cessé d'utiliser le VPOt et d'une période de 2 ans de préparation et de communication par et au sein de l'IMEP, des organisations partenaires, des fabricants de VPO et des gouvernements des pays et des territoires. Le soutien actif des hauts responsables de l'IMEP et des ministères de la santé nationaux a été crucial, de même que la coopération de tous les fabricants de VPO pour cesser la production et la distribution de VPOt et assurer la disponibilité et la livraison en temps utile du VPOb. Combiné à l'éradication du PVS, le retrait final de tous les VPO permettra de parvenir à un monde exempt de poliomyélite.

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MEASLES AND RUBELLA GLOBAL STRATEGIC PLAN 2012-2020 MIDTERM REVIEW

TABLE OF CONTENTS

Measles and Rubella Global Strategic Plan 2012-2020 Midterm Review.....	1
Midterm review team members	1
Key highlights	1
Section 1. Background, context and rationale for midterm review	2
Section 2. Methodology of midterm review.....	7
Section 3. Overarching conclusions.....	7
Section 4. Regional summaries.....	9
Section 5. Core strategies, building on the polio transition, governance and resource mobilization.....	19
Section 6. Summary.....	50

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KEY HIGHLIGHTS

1. Eradication is the ultimate goal but it is premature to set a date for its accomplishment. Existing regional elimination goals should be vigorously pursued to enable setting a global target by 2020.
2. The basic strategic approaches articulated in the *Global Measles and Rubella Strategic Plan 2012-2020* are valid to achieve the goals but have not been fully implemented (or not appropriately adapted to local situation).
3. The report recommends a shift from primary reliance on supplementary immunization activities (SIAs) to assure two doses of measles-containing vaccine (MCV) are delivered to the target

Measles Rubella Midterm Review Report

- population to primary reliance on ongoing services to assure administration of two doses of MCV. Regular high quality SIAs will still be necessary while ongoing services are being strengthened.
4. The report recommends a shift from primary reliance on coverage to measure progress to incorporating disease incidence as a major indicator.
 5. The report recommends that the measles/rubella vaccination program be considered an indicator for the quality of the overall immunization program and that measles/rubella incidence and measles and rubella vaccination coverage be considered as primary indicators of immunization program performance.
 6. Polio transition presents both risks and opportunities: risks should be minimized and opportunities maximized.
 7. A school entry immunization check could contribute significantly to strengthening overall immunization services with assurance that recommended doses of measles and rubella vaccines as well as other vaccines have been delivered and providing those vaccines at that time if the child is un or under-vaccinated.
 8. Program decisions should increasingly be based on good quality data and appropriate analysis.
 9. The incorporation of rubella vaccination into the immunization program needs to be accelerated - it should be accorded equivalent emphasis as measles.
 10. Outbreak investigation and response are critical but the most important thing is to prevent outbreaks.

SECTION 1. BACKGROUND, CONTEXT AND RATIONALE FOR MIDTERM REVIEW

Disease and Vaccines

Measles, a viral illness, is one of the most highly infectious diseases known to man. Complications of measles include pneumonia, diarrhea and encephalitis. Case fatality rates from measles vary from 0.1% in the developed world to 15% in the less developed world,¹ with death usually caused by pneumonia or diarrhea. Population immunity of 92% – 95% is considered necessary to stop measles transmission.² A highly-effective measles vaccine has existed since 1963. Nonetheless, in 2014, an estimated 114,900 people, mostly children, died from the disease³. Due to its highly infectious nature, measles effectively seeks out unvaccinated individuals. For this reason, it is often considered to be the indicator disease or the ‘canary in the coal mine’, able to identify individuals and subpopulations who remain unreached by immunization programs. Measles vaccination coverage serves as an indicator of the quality of immunization programs,⁴ while the epidemiology of measles cases highlights specific geographic areas and populations in which immunization services require further strengthening.

Rubella, another vaccine-preventable viral disease, is primarily a concern because infection during pregnancy can result in severe congenital defects in the baby. These congenital defects include heart

¹ Strebel PM, Papania MJ, Fiebelkorn AP, Halsey N. Measles vaccine. In Plotkin SA, WA Orenstein, PA Offit (Eds.), *Vaccines*, 6th Edition, China: Elsevier Saunders 2013.

² Orenstein WA, Gay NJ. The Theory of Measles Elimination: Implications for the Design of Elimination Strategies. *Journal of Infectious Diseases*, 2004, 189(Suppl 1): S27-S35.doi: 10.1086/381592

³ CDC. Progress toward Regional Measles Elimination – Worldwide. 2000-2014.MMWR 2015; 64(44);1246-1251

⁴⁴ <http://www.gavi.org/results/goal-level-indicators/health-systems-goal-indicators/> Accessed July 10 2016

defects, cataracts, deafness, and cleft palate among others. In 2010, more than 100,000 babies with congenital rubella syndrome (CRS) were estimated to be born globally.⁵

The concept of measles eradication has been reviewed by the International Task Force for Disease Eradication (ITFDE), as well as by an independent group of experts and the World Health Organization's (WHO's) Strategic Advisory Group of Experts on Immunization (SAGE), resulting in the affirmation of the feasibility and desirability of eventual eradication of measles. The ITFDE also reviewed progress towards rubella eradication, concluding that this was technically feasible and that the economic literature demonstrated that eradication of both measles and rubella was more cost effective than indefinite high level control of either of these diseases.^{6 7 8}

When the Expanded Programme on Immunization (EPI) was launched in 1974, measles vaccine was one of the six vaccines included in the basic package of vaccines recommended for all children in developing countries. As injectable vaccines recommended at either 9 months or 12-15 months of age, measles containing vaccines (MCV) (measles (M), measles rubella (MR), measles mumps rubella (MMR), and measles mumps rubella varicella (MMRV) are currently part of the schedule of childhood vaccinations in all countries. Mass vaccination campaigns against measles (also called supplementary immunization activities, or SIAs, because they aim to reach children missed by routine immunization activities) targeting all persons in a given age group (usually children ≥ 9 months of age) regardless of prior vaccination status were pioneered by the Pan American Health Organization (PAHO) in Latin America. These SIAs have remained an integral part of national and global immunization program activities but should be regarded as truly supplemental, with primary emphasis on delivering two doses of MCV to all children through ongoing services.

Relationship of measles and rubella control and elimination to other global health initiatives

The control and elimination of measles and rubella contribute directly to achieving the goals of numerous global health initiatives. Programs to eliminate measles and rubella are significant contributors to achieving the health-related Sustainable Development Goals and targets.⁹ The World Health Assembly (WHA) in May 2016 (Resolution WHA 69.11) recognized that universal health coverage includes access to essential vaccines, and it reaffirmed the commitment to accelerate progress in reducing newborn, child and maternal mortality by ending all such preventable deaths before 2030.

This report's emphasis on the need to improve surveillance should serve to strengthen national surveillance and response capacities in line with requirements in the International Health Regulations

5Vynnycky E, Adams EJ, Cutts FT, Reef SE, Navar AM, Simons E et al. Using seroprevalence and immunization coverage data to estimate the global burden of congenital rubella syndrome, 1996-2010: a systematic review, 2016 (<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0149160>)

⁶World Health Organization. Meeting of the international task force for disease eradication, November 2015. *Weekly Epidemiological Record*, 2016, 91:61-71.

⁷World Health Organization. World Health Organization global technical consultation to assess the feasibility of measles eradication. 2010
http://www.who.int/immunization/sage/1_Global_Technical_Consultation_Assess_Feasibility_Measles_Erad_8_sept_2010.pdf?ua=1. Accessed September 18, 2016

⁸World Health Organization. Meeting of the Strategic Advisory Group of Experts on Immunization, November 2010. Summary, conclusions and recommendations. *Weekly Epidemiological Record*, 2011,86:1-16

⁹United Nations. Sustainable development knowledge goals- Transforming our world- the 2030 agenda for sustainable development (<https://sustainabledevelopment.un.org/?menu=1300> Accessed July 10 2016).

Measles Rubella Midterm Review Report

(2005) (IHR)¹⁰ A fundamental aspect of the IHR is the obligation for all 196 countries that are party to the Regulations (i.e., two countries beyond the 194 Member States of WHO) to develop, strengthen and maintain core public health capacities for surveillance and response in order to be able to detect, assess, notify and report events and respond to public health risks and emergencies of international concern.

The effort to eliminate measles and rubella, which builds on and enhances the overall immunization system, also serves to enhance global health security. At the Ise-Shima Summit in May 2016, the G-7 countries repeated their commitment to advancing compliance with WHO's IHR objectives including through the Global Health Security Agenda (GHSa).¹¹ GHSa measures progress for its Immunization Action Package by achieving at least 90% coverage of the country's fifteen-month-old population with at least one dose of MCV, as demonstrated by coverage surveys or administrative data.¹² The desired national impact is to have effective protection through achievement and maintenance of immunization against measles and other epidemic-prone vaccine preventable diseases (VPDs). Measles immunization is emphasized because it is widely recognized as a proxy indicator not only for overall immunization coverage levels, but also of the level of effectiveness of the primary health care system in general. While implementing the recommendations made in this report most obviously supports the implementation of the GHSa's Immunization Action Package, it also supports a number of other GHSa Action Packages. High levels of measles control contribute to combating antimicrobial resistant bacteria, one area of focus of the GHSa, by decreasing the inappropriate use of antibiotics and the need to appropriately use antibiotics to treat measles complications caused by secondary bacterial infections, such as bacterial pneumonia. This report's focus on laboratory-supported surveillance and appropriate interpretation and use of surveillance data is aligned with the GHSa's efforts to increase laboratory capacity at national, provincial and district levels while linking to national disease reporting frameworks, as well as with the GHSa's Real-Time Surveillance Action Package and the GHSa's Workforce Development Action Package.¹³

Other relevant international frameworks are the Convention for the Rights of Children,¹⁴ and the Sphere project (Sphere) recommendations.¹⁵ Sphere articulates measles vaccination as one of the highest priorities in humanitarian emergencies due to the deadly nature of outbreaks in these settings. Recent data from the United Nations Children's Fund (UNICEF) indicate that almost two-thirds of the world's under- or unvaccinated children now live in conflict zones.¹⁶

Development and Implementation of the *Global Measles and Rubella Strategic Plan 2012-2020*

In 2001, the Measles Initiative, a coalition led by UNICEF, WHO, the US Centers for Disease Control and Prevention (CDC), the United Nations Foundation (UNF), and the American Red Cross (ARC), was formed, spearheading a more aggressive approach to measles control based on the PAHO strategy of wide age-

¹⁰ World Health Organization. International Health Regulations 2005. Second edition.(http://apps.who.int/iris/bitstream/10665/43883/1/9789241580410_eng.pdf)

¹¹ G7 Ise-Shima vision for global health 2016 (<http://www.g8.utoronto.ca/summit/2016shima/health.html>) Accessed July 26 2016. Accessed August 15 2016.

¹² Global Health Security Agenda (<https://ghsagenda.org/>, Accessed July 26, 2016.

¹³ Global Health Security Agenda: Action Packages. Available at <https://ghsagenda.org/packages.html> Accessed Sept 8 2016.

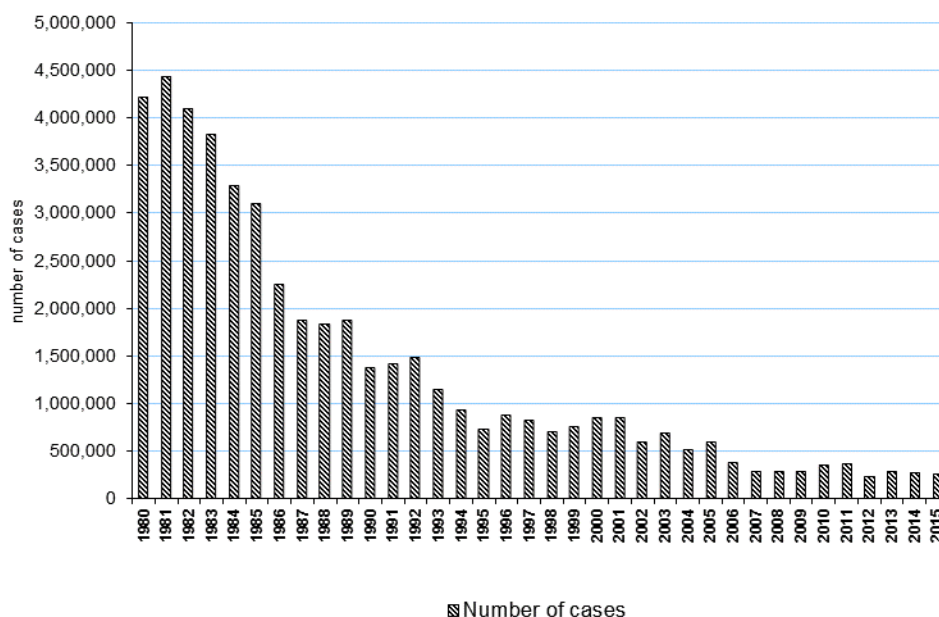
¹⁴ United Nations Human Rights- Convention of the Rights of the Child. 1989 (<http://www.ohchr.org/EN/ProfessionalInterest/Pages/CRC.aspx>. Accessed July 10 2016.

¹⁵ The SPHERE Project. Humanitarian Charter and Minimum Standards in Humanitarian Response <http://www.sphereproject.org/handbook/>, Accessed July 10 2016.

¹⁶ UNICEF- Two-thirds of unimmunized children live in conflict-affected countries – UNICEF, 2016 http://www.unicef.org/media/media_90987.html, Accessed July 10 2016.

Measles Rubella Midterm Review Report

range national SIAs and regular follow-up SIAs as a supplementary strategies to increasing routine first and second dose coverage with MCV. This strategy was initially highly successful and resulted in a reduction of estimated measles mortality by 74% in 2010 relative to 2000.¹⁷ However, since that time, gains have slowed with a plateauing of global coverage with the first dose of measles containing vaccine (MCV1) and SIA coverage inadequate to stop the accumulation of individuals susceptible to measles, reflected in a plateauing of the number of reported cases globally (Figure 1).



Source: WHO/IVB database, 2016
194 WHO Member States.
Data as of 15 July 2016

Figure 1. Number of measles cases reported to WHO by year, 1980 – 2015. Data as of 9 July 2016

In 2012, the Initiative, now targeting both measles and rubella and renamed the Measles and Rubella Initiative (M&RI), published the '*Global Measles and Rubella Strategic Plan 2012-2020*'.¹⁸ This document had, as a goal for end-2020, to achieve measles and rubella elimination in at least five WHO regions. Five core strategies to reach this goal were articulated, as follows:

- Achieve and maintain high levels of population immunity by providing high vaccination coverage with two doses of measles- and rubella-containing vaccines;
- Monitor disease using effective surveillance and evaluate programmatic efforts to ensure progress;
- Develop and maintain outbreak preparedness, respond rapidly to outbreaks and manage cases;
- Communicate and engage to build public confidence and demand for immunization;
- Perform the research and development needed to support cost-effective operations and improve vaccination and diagnostic tools.

¹⁷ Simons E, Ferrari M, Fricks J, Wannemuehler K, Anand A, Burton A et al. Assessment of the 2010 global measles mortality reduction goal: results from a model of surveillance data. *Lancet*, 2012, 379:173-2178.

¹⁸ World Health Organization. Global Measles and Rubella Strategic Plan: 2012-2020 (http://apps.who.int/iris/bitstream/10665/44855/1/9789241503396_eng.pdf).

Measles Rubella Midterm Review Report

To measure progress toward the 2020 goal, specific milestones for 2015 were established. These were to:

- Reduce annual measles incidence to less than five cases per million and maintain that level;
- Achieve at least 90% coverage with the first routine dose of measles-containing vaccine (or measles-rubella-containing vaccine as appropriate) nationally, and exceed 80% vaccination coverage in every district or equivalent administrative unit;
- Achieve at least 95% coverage with M, MR or MMR during SIAs in every district;
- Establish a rubella/CRS elimination goal in at least three additional WHO regions (i.e., in addition to the AMR and EUR that had established goals before 2012);
- Establish a target date for the global eradication of measles.

Figure 2 summarizes the status of these milestones based on 2015 data.

2015 Milestone	2015 Data	Evaluation
Reduce annual measles incidence to less than five cases per million and maintain that level	Global incidence of 39.3 per million	
Achieve at least 90% coverage with the (or measles- rubella-containing vaccine as appropriate) nationally, and exceed 80% vaccination coverage in every district or equivalent administrative unit.	119 (61%) countries have coverage with first dose of measles containing vaccine exceeding 90% at national level.	
Achieve at least 95% coverage with measles, measles rubella or measles mumps rubella vaccine during supplementary immunization activities (SIAs) in every district.	Of 34 countries conducting SIAs between 2012 and 2014 and conducting coverage evaluations of the SIA, 16 (47%) reached 95% national coverage	
Establish a rubella/congenital rubella syndrome elimination goal in at least three additional World Health Organization regions (i.e., in addition to the Region of the Americas and the European Region that had established goals before 2012).	One additional region, the Western Pacific Region, has established a rubella elimination goal but no date is associated with it	
Establish a target date for the global eradication of measles.	No target date for global measles eradication established	

Figure 2. Status of Global Measles and Rubella Strategic Plan: 2012-2020 2015 Milestones

Legend: Black: Little or no progress.

Gray: Moderate progress but inadequate to meet 2015 milestone

Recommendation for Midterm Review

In 2015, WHO's SAGE recommended a midterm review (MTR) of the *Global Measles and Rubella Strategic Plan*. The objectives of the MTR are to:

Measles Rubella Midterm Review Report

- provide a candid review of progress towards, and key political, financial and technical reasons for not attaining, 2015 World Health Assembly targets and regional elimination goals;
- assess the quality of implementation of the *Global Measles and Rubella Strategic Plan's 2012-2020's* five key strategies and provide recommendations on how the strategies and principles should be refined to address weaknesses in immunization systems and to accelerate progress towards the global and regional goals;
- formulate a set of lessons learned, risks, and financial, political and programmatic priorities over the next five years (2016-2020) for countries and partners in order to execute the work.

The request for the MTR reflects the urgency of re-setting the course to reach the 2020 goals. This urgency is dictated by the fact that Global Polio Eradication Initiative (GPEI) assets, which have been pivotal in the gains made toward measles and rubella elimination through the contribution of human resources and infrastructure, will decrease rapidly as of 2017 (Figure 11, page 68) if concrete and funded plans for transition are not made. Furthermore, the current status of measles control leads to a situation in which susceptibility to measles is distributed across increasingly wide age groups, which will make eventual elimination both more expensive and more technically difficult. Incomplete control allows persons to grow to older ages still susceptible as they have neither been vaccinated nor exposed to measles because while not eliminated, measles incidence is decreased. This can lead to outbreaks which have wider age ranges of cases than in the pre-vaccine era.

SECTION 2. METHODOLOGY OF MIDTERM REVIEW

The MTR was conducted by a project team of five individuals. The team undertook a comprehensive document review, and conducted interviews with and received presentations from a broad range of stakeholders. Each individual (with the exception of the chairperson) was tasked with contacting specific Regional Offices of WHO to develop an in-depth understanding of the Region's experiences in pursuing measles elimination and rubella control. Each Office also selected one or two countries from its region to illustrate the diverse faces of measles elimination and rubella control. A brief summary of regional findings is given below, in Section 4. Detailed regional and country reports are available in the web-based version of this report.

This report examines each of the *Plan's* five strategies. For each strategy, the report summarizes relevant background, progress and challenges to date, the deliberations of the MTR team, and recommendations for mid-term corrections. In addition, in the context of measles and rubella elimination, the report addresses the critical questions of building on the polio transition, governance, and resource mobilization.

SECTION 3. OVERARCHING CONCLUSIONS

This review reached a number of overarching conclusions, articulated below.

- The *Global Measles and Rubella Strategic Plan, 2012 – 2020* set the ambitious goal of achieving measles and rubella elimination in at least five World Health Organization (WHO) regions by 2020 through the implementation of five core strategies. Significant gains toward measles elimination have been made in the past 15 years with an estimated 79% reduction in global measles mortality between 2000 and 2014 resulting in over 17 million measles-related deaths averted. From 2012 – 2014, alone, over four million measles-related deaths are estimated to have been averted through measles vaccination. During 2012-2015, the number of WHO Member States providing a second

Measles Rubella Midterm Review Report

dose of measles containing vaccine (MCV2) nationally through routine immunization services increased from 131 (68%) to 154 (79%) and estimated global MCV2 coverage increased from 48% to 56%. By end 2015, Regional Verification Commissions (RVCs) in the American, European and Western Pacific Regions had verified elimination of measles in 61 Member States (34/35 Member States in the Americas; 21/53 Member States in Europe; and 6/27 Member States in the Western Pacific) and elimination of rubella in 67 Member States (35/35 Member States in the Americas; 20/53 Member States in Europe).

- Although all six regions now have measles elimination goals by 2020 and two have rubella elimination goals by this date, recent years have seen a slowing of progress. No region except the Americas has yet achieved its 2015 milestones. All countries should continue to work toward these elimination goals with a particular focus on strengthening routine immunization systems.
- The basic strategies – i.e., surveillance, achieving high levels of population immunity, outbreak prevention and control, research, and communications – articulated in the *Plan* are sound, however, these require full implementation, and, at times, adaptation to the local context. The main impediments to full implementation have been inadequate country ownership and global political will, reflected in inadequate resources.
- Despite the recent, welcome increase in funding for measles and rubella vaccination from Gavi, The Vaccine Alliance (Gavi), the measles and rubella program remains under-resourced both from the financial and the human resource perspectives, both at global and at regional level.
- Although both the tools and the strategies to reach the 2020 goals currently exist, the further development of certain tools, e.g., microarray patches (MAPs), could enhance the likelihood of success.
- Although all six regions have measles elimination goals and three regions have rubella elimination goals¹⁹ with the ultimate vision of a world free of measles and rubella, it is premature to set a timeframe for eradication of either disease at this point. Instead, the annual review of progress toward the Global Vaccine Action Plan (GVAP) goals²⁰ should be used to assess progress toward measles elimination. A determination should be made, not later than 2020, whether formal global goals for measles and rubella eradication should be set with timeframes for achievement. In the meantime, all regions should work toward achieving the regional elimination goals.
- Strengthening of immunization systems is critical to achieving regional elimination goals. Working to achieve measles and rubella elimination can help strengthen health systems in general and immunization systems in particular – this should be carefully documented. Measles and rubella vaccination programs should be considered ‘indicator programs’ for immunization systems, and the incidence of measles and rubella and coverage with measles and rubella vaccines should be considered among the primary indicators of immunization system performance. Coverage with the first dose of measles containing vaccine (MCV1) should be adopted as an indicator in the Global Vaccine Action Plan (GVAP) to align with the prioritizing of

¹⁹ Two of these regions have a rubella elimination date by 2020 while one does not yet have a date associated with the goal.

²⁰ GVAP has as measles and rubella targets to achieve measles elimination in four WHO regions and rubella elimination in two WHO regions by 2015, and to achieve measles and rubella elimination in five WHO regions by 2020. World Health Organization. *Global Vaccine Action Plan 2011-2020*. Available at http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/ Accessed September 18 2016.

Measles Rubella Midterm Review Report

this indicator by the International Health Regulations, Global Health Security, and Gavi, The Vaccine Alliance.

- Measles and rubella elimination efforts should be aligned with and take advantage of changing global priorities and opportunities, for example the transition of polio assets (see below).
- Measuring coverage with measles and rubella containing vaccines, while important, is not the best indicator of progress towards measles/rubella control/elimination. Disease incidence, in the presence of an effective surveillance system, is the most important indicator of progress. The presence or absence of measles is one of the best indicators of overall immunization program performance.
- There is an urgent need to strengthen the collection and use of surveillance data to better guide program strategy and implementation.
- An implementation plan in response to these recommendations should be developed not later than twelve months after the release of this report.
-

SECTION 4. REGIONAL SUMMARIES

Table 1 summarizes regional incidence of measles reported through the Joint Reporting Form (JRF) for the period 2013 – 2015, as well as presenting data on 2010 as a baseline. Table 2 presents similar data for rubella. A brief summary of the current status of measles and rubella control in each of WHO's regions follows these Tables.

WHO region	MCV1 national coverage (%)					% of Member States reporting measles in their JRF					Measles incidence per million population					% of Member States with incidence less than 5 per million population				
	2015	2014	2013	2010	% change 2010–2015	2015	2014	2013	2010		2015	2014	2013	2010	% change 2010–2015	2015	2014	2013	2010	% change 2010–2015
African Region	74	72	71	73	+1.4	98	100	100	98		115.3	76.7	182.5	233.0	-51	51	51	53	30	+71
Region of the Americas	94	93	92	92	+1.1	97	100	97	100		0.6	2.0	0.5	0.3	+100	94	97	97	100	-6
Eastern Mediterranean Region	76	76	76	81	-6.6	95	90	86	100		33.5	28.9	34.7	17.5	+91	38	24	24	38	0
European Region	94	94	95	93	+1.1	77	77	87	98		36.3	19.2	33.6	34.2	-6	53	45	58	68	-22
South-East Asia Region	85	85	84	83	+2.4	91	81	100	100		17.4	17.9	16.0	29.9	-42	45	45	45	36	+25
Western Pacific Region	96	97	97	96	0	59	63	74	93		35.4	71.6	17.5	27.6	+28	33	22	48	63	-47
Total	85	84	84	85	0	86	87	91	97		39.3	39.8	40.2	50.0	-21	55	51	58	59	-6

Table 1. Number of measles cases and incidence by WHO region, 2013 - 2015 and baseline 2010.

^a List of Member States not reporting JRF measles data: Albania, Andorra, Cook Islands, Fiji, Finland, Greece, Indonesia, Kiribati, Libya, Marshall Islands, Mauritius, Monaco, Montenegro, Nauru, Netherlands, Niue, Oman, Poland, Portugal, Samoa, San Marino, Singapore, Solomon Islands, Turkey, Tuvalu, Ukraine, United States of America. (NB: Turkey, Ukraine and Tuvalu submitted their JRF after the 24th June 2016, date of GVAP report).

Source: JRF (as of 24 June 2016) and WHO-UNICEF estimates, 1980–2015, revision July 2016.

WHO region	National rubella coverage (%)				Member States reporting rubella cases (%) ²¹				Rubella incidence per million population			
	2015	2014	2013	2010	2015	2014	2013	2010	2015	2014	2013	2010
African Region	12	9	4	0	94	94	91	79	5.6	7.8	15.1	3.9
Region of the Americas	94	93	92	93	97	100	97	100	0.0	0.0	0.0	0.0
Eastern Mediterranean Region	45	42	38	38	86	90	86	81	3.0	4.7	6.6	3.5
European Region	94	94	95	93	72	72	81	92	0.6	1.0	62.8	14.3
South-East Asia Region	14	12	12	3	82	91	100	82	2.6	5.0	5.5	26.1
Western Pacific Region	89	90	88	61	56	59	67	85	5.1	7.0	18.5	27.1
Total	46	44	42	35	81	84	86	88	3.3	4.8	14.9	15.0

Table 2. Rubella cases and incidence by WHO region, 2013 - 2015 and baseline year 2010.

Note: MCV1 was used as a proxy in the Member States that have introduced rubella vaccine.

Source: JRF (as of 24 June 2016) and WHO-UNICEF estimates, 1980–2015, revision July 2016.

²¹ This percentage is of all countries (with or without rubella surveillance) who report rubella cases.

African Region (AFR)

Status

Regional measles mortality reduction activities began in AFR in 2001 and, ten years later, all 47 countries adopted the target of measles elimination by 2020. Although there is no target date set for rubella elimination, countries are introducing rubella containing vaccine (RCV) and conducting surveillance for rubella and CRS.

Significant progress has been achieved to date. The number of countries achieving MCV1 coverage of 90% or more increased from 4 in 2000 to 16 in 2009, leading to an increase in regional MCV1 coverage from 53% to 74% during the same period. As of 2014, 14 countries had maintained > 90% coverage with MCV1. Nonetheless, regional coverage has stagnated around 75% since 2009. Introduction of MCV2 and RCV has also made progress: by December 2015, 23 (48.9%) of 47 countries had introduced MCV2 and 9 (19%) had introduced RCV in their routine immunization programs. In response to higher vaccination coverage, reported cases of measles declined > 90% from more than half a million annually in 2000 to fewer than 50,000 in 2008. Despite this progress, 2010 and 2011 saw sharp increases in reported cases due to outbreaks. These outbreaks were predominantly in Southern African countries with transmission primarily in older age groups. Further increases in cases in 2013 represented large outbreaks occurring in the Democratic Republic of the Congo and Nigeria which, between them, accounted for 83% of the 171,178 cases reported in AFR that year. Overall, the average incidence for the period 2012-2014 of reported cases was less than 1 per million population in 11 countries, between 1 and 5 per million in another 11, between 5 and 9 in 6 countries, and between 10 and 49 in 12 countries. Four countries (Ethiopia, Nigeria, Angola, and Namibia) had an average annual incidence above 50 per million. During the period reviewed, the larger countries have faced outbreaks of varying magnitude almost annually. In Africa, no RVC currently exists.

By 2015, case-based surveillance had been implemented in 44 countries. AFR does not monitor the percentage of districts reporting at least two cases of non-measles rash fever cases. However, it does monitor other indicators of surveillance quality. These include the percentage of cases with adequate specimens collected (2012: 91%; 2013: 78%; 2014: 85%; 2015: 82%). As case-based surveillance has improved throughout the continent, the number of specimens received in the network laboratory has steadily increased.

Despite great progress in vaccination coverage and surveillance since 2000, substantial challenges to reaching elimination remain. The major challenges are gaps in population immunity at subnational levels, immunity gaps among older children, lack of resources to fully implement recommended strategies, suboptimal performance during SIAs and lack of political commitment and competing priorities at national level. In addition, because of the large contribution that polio funding makes to supporting measles and rubella activities in AFR, this region is particularly vulnerable to decreases in GPEI funding.

Conclusions and Recommendations

The diverse socio-economic development levels, political structures, and health system challenges in AFR influence immunization program performance overall as well as the ability to achieve measles elimination. Twelve (25.7%) of 47 countries with strong programs have sustained very low incidence of measles and are nearing measles elimination while 16 (34%) countries have immunity and surveillance gaps at subnational level but are on track for elimination. Eight (17%) countries with a variety of

program gaps, including large population immunity gaps and poor surveillance (including lack of program ownership) are not on track for measles elimination. Lastly, there are 11 (23%) countries with major challenges such as large populations, insecurity, high incidence of measles, frequent outbreaks and leadership gaps. These countries pose the biggest challenge to reaching elimination in the region.

While the strategies for measles elimination are appropriate, the failure to meet the set mid-term goals is due to incomplete implementation of the strategies. Technical issues, such as improved surveillance, higher quality SIAs and better monitoring, can be addressed. However, addressing technical issues alone is not adequate: an enabling environment, with local and national commitment, improved health systems performance and adequate resources will be required. Region-specific recommendations are as follows:

- Give priority to the introduction of MCV2 in all countries;
- Establish and maintain elimination level surveillance at subnational level in all countries;
- Make financial support for all SIAs in the region contingent on the ability to meet minimum standards of readiness to ensure the highest quality of activity;
- Continue to make outbreak investigation a priority with the objective of identifying the reasons for the outbreak and the chains of transmission so as to guide local strategies;
- Systematically use surveillance data and outbreak investigation findings for advocacy with local and national stakeholders and
- Undertake an in-depth review of program activities for the coming years to define the most appropriate strategy and the technical and financial support needed in the countries identified as presenting the biggest challenge to meeting the regional elimination goal.

Americas Region (AMR)

Status

AMR achieved measles elimination in 2002 and rubella/CRS elimination in 2009, convincingly demonstrating the feasibility of eliminating these conditions across a large and diverse region. Elimination was achieved through strong political commitment and leadership, regional cohesion, effective disease surveillance, and a combination of strong routine immunization programs and mass vaccination campaigns. In 2014, in addition to the U.S. and Canada, 23 (70%) of the other 33 countries in AMR reached national coverage of $\geq 90\%$ with the first dose of measles mumps rubella vaccine (MMR1), with 18 (78%) of those 23 countries reporting that $\geq 80\%$ of districts achieved $\geq 90\%$ coverage. The second dose of measles mumps rubella vaccine (MMR2) has been introduced into 30 of the 35 countries in the region, and in 2014, 15(55%) of 27 countries submitting data using the WHO/UNICEF Joint Reporting Form achieved national coverage of $\geq 90\%$, with 12 countries reporting that $\geq 80\%$ of districts achieved $\geq 90\%$ coverage with MMR2. Sensitive and timely case-based surveillance for measles, rubella, and CRS is in place in all countries in AMR, although a decrease in performance with regard to various indicators was observed between 2014 and 2015, and the quality of the active epidemiological surveillance is not homogenous at the sub-national and local levels.

Since elimination of measles was achieved in 2002, importations of measles virus have led to multiple outbreaks, producing a total of 5,277 cases between 2003 and 2014 and an additional 614 cases in 2015. Large outbreaks with multiple generations of cases have occurred in Canada, the U.S., and Brazil. The outbreak in Brazil lasted a total of 28 months, ultimately resulting in 1,052 reported cases in 38 municipalities. As endemic measles transmission is defined as the existence of any continuous

indigenous chain of transmission of measles virus that persists for >1 year in any defined geographic area,²² this outbreak in Brazil was considered re-establishment of endemic measles. Of the cases in Brazil, 73% were in unvaccinated individuals and 9% were in individuals of unknown vaccination status; of the vaccinated individuals who contracted measles, only 7% had received two doses of vaccine. Almost half (44%) of the persons with measles who had not been vaccinated against measles were 15-39 years of age. On July 6th 2015, Brazil reported the last endemic measles case. One year later, following a review of data, the RVC declared Brazil free of endemic measles virus. This outbreak demonstrated that low levels of measles virus transmission can persist in populations with high reported vaccination coverage and that importations of measles virus remain a threat

The RVC for AMR, known as the International Expert Committee for Measles and Rubella Elimination in the Americas, initially met in Dec. 2010. Annual meetings were held after that with the last meeting to date held in 2015. An ad hoc meeting was held in September, 2014.

Conclusions and Recommendations

The current status of AMR documents that the region continues to lead in the global effort to eliminate measles and rubella, demonstrating the feasibility of global eradication. Although the components required to achieve regional elimination are in place, threats to maintaining a region free of measles and rubella in our interconnected world, such as the importations of both viruses, are certain to continue to occur for years to come. The recent measles outbreaks in the region demonstrated that immunity gaps persist, despite high reported vaccine coverage. Simultaneously, new threats (e.g. Zika virus) are competing for limited public health and clinical resources, adding to the difficulty of maintaining strong population-wide immunization programs. Other problems alluded to by AMR Office (AMRO) staff include high turnover of staff, inadequate planning and supervision of vaccination campaigns, difficulties and delays in providing laboratory supplies and reagents and growing vaccine hesitancy.

Priority activities for the region include ongoing work to ensure a high level of country ownership of and political support for immunization activities, including routine immunization, strengthened surveillance for measles, rubella, and CRS and well-planned and well-executed follow up vaccination campaigns to help reduce or eliminate immunity gaps. In addition, the region needs to maintain the capacity to detect and respond rapidly and aggressively to all suspected cases of measles, rubella, and CRS, increasing the quality of surveillance indicators, guarantee sufficient availability of laboratory supplies and reagents to maintain the quality of its network of laboratories, continue to develop new surveillance tools, and disseminate technical guidelines and training materials throughout the region.

PAHO's Member States have recently submitted updated data regarding measles to the RVC. The region hopes to be declared measles-free by end -2016.

Eastern Mediterranean Region (EMR)

Status

EMR initially set 2010 as a target date for elimination of measles and has subsequently revised that date twice, to 2015 and then 2020; it is not likely to meet the current target. EMR has yet to set a target date for the elimination of rubella, but has proposed setting one in 2020.

²² Orenstein WA, Papania MJ. Defining and Assessing Measles Elimination Goals. *Journal of Infectious Diseases*, 2004, 189(Suppl 1): S23-S26.

Measles Rubella Midterm Review Report

In 2015, the reported incidence of measles in EMR remained high. WHO's joint reporting form gives a regional incidence of 33.5 cases per million. In 2015, only eight (38%) of the 21 countries in the region had met the indicator of a reported measles incidence of < 5 cases/million population. The number of estimated measles deaths in the region in 2014, while 74% lower than in 2000, was 13,900. Reliable information concerning rubella and CRS cases in the region is not available, although some countries do have case-based surveillance for these conditions.

As summarized in their status report, of the 22 countries in EMR, only 11 (50%) had achieved MCV1 coverage of $\geq 90\%$ nationally and in $\geq 80\%$ of districts in 2014. MCV1 coverage for the region has been stagnant over the past decade at approximately 75-80%. MCV2 coverage has been steadily rising since 2000, but was still under 70% in 2014. All but five countries in the region have introduced RCV.

Despite high coverage with MCV1 and MCV2 (based on administrative data) and repeated earlier measles SIAs, Egypt experienced a drop in routine immunization coverage and population immunity, and as a result experienced a small measles outbreak in 2012 and a large measles outbreak in 2014-15, with the latter outbreak persisting for > 18 months. The vast majority of the cases in 2014-15 were in unvaccinated children < 5 years of age, reflecting a drop in routine immunization coverage due to a combination of a shortage of MMR vaccine and civil unrest, together with a six-year interval since the last SIA in 2009.

In 2014, relatively few countries in EMR had met all of the measles and rubella surveillance indicators.

Despite substantial problems with security in a number of countries in EMR, many countries in the region conducted measles SIAs in 2014 and 2015, often co-administering Vitamin A and occasionally offering other interventions. Approximately two-thirds of countries in the region provide at least 80% of operational costs for SIAs, although the quality of the SIAs has been variable.

There is currently no RVC in EMR.

Conclusions and Recommendations

The report from EMR demonstrates the very difficult hurdles to achieving measles and rubella elimination in this region of the world. While some small and relatively wealthy countries in the region have achieved national elimination of measles, rubella, and CRS, other countries have found it difficult to achieve and sustain high levels of population immunity through a combination of a strong routine immunization program and well-organized SIAs. Many of the same countries have been unable to achieve targets concerning surveillance indicators. In most of the countries in the region that have not been able to achieve and sustain high levels of MCV1 and MCV2 (and RCV) coverage, diverse societal problems make it difficult to reach all segments of the population on a regular basis. These problems include war, civil unrest, political and economic instability, ethnic and religious strife, and migration of a large number of migrants and internally displaced persons, among others. In such settings, the obstacles to the elimination of measles, rubella and CRS are formidable.

Despite the many challenges, as EMR Office (EMRO) staff understands, there needs to be ongoing commitment to improving the quality and reach of routine immunization services, linking them to other infant and child health programs whenever possible. At the same time, the planning, implementation, and follow-up assessment of well-targeted and timely SIAs need to be supported technically and financially in high priority countries in the region. In addition, impediments to the availability of MRCV and of laboratory supplies and reagents need to be minimized and case-based surveillance systems

improved, so as to ensure timely detection of and response to outbreaks. Finally, renewed political commitment to and visibility of measles and rubella elimination goals is needed in multiple countries.

European Region (EUR)

Status

EUR set the goal of reaching measles and rubella elimination and prevention of CRS by 2015. All 53 countries in the Region have two doses of MRCV in their routine immunization schedules. In 2015, reported regional coverage with MCV1 was 94% with little change in the past four years. District level data are not currently available from all countries.

Significant measles outbreaks were reported in 2013 and in 2014 in Azerbaijan, Bosnia and Herzegovina, Georgia, Germany, Italy, Latvia, the Netherlands, Russian Federation, Turkey, Ukraine and the United Kingdom. There is a continuing large outbreak of rubella in Poland, although the number of cases began to decline in 2014. Most recent outbreaks of measles and rubella have occurred among the general population but some have been focused on recognized under-vaccinated groups. The EUR uses indicators which differ from those used in other regions to monitor the quality of surveillance. The RVC in EUR was first convened in 2012 and held annual meetings in 2013, 2014 and 2015, for a total of four meetings to date. A fifth meeting is scheduled for October 2016. The RVC meeting of October 2015 concluded that 21 (40%) of 53 Member States had eliminated measles and 20 (38%) had eliminated rubella.

Conclusions and Recommendations

Discussions with EUR Office (EURO) staff identify the following three main barriers to achieving measles and rubella objectives: 1) inadequate political commitment – both at the national (Presidential or Ministerial) level and at the health system level; 2) population attitudes to immunization – most are not against immunization but are apathetic about immunization, and do not perceive any personal risk from VPDs; and, 3) diversity of population and health systems in the Region. The 5 – 10% of the population that remains susceptible to measles appears to be sufficient to sustain transmission. This population is very diverse in the Region and requires different approaches to reach with vaccination. Elimination of measles and rubella transmission by 2020 is feasible in the European Region, but it seems unlikely it will be achieved.

- Sixty percent of countries in the region have achieved interruption of measles and rubella transmission in 2015.
- Some of the largest and most developed countries (e.g., France, Germany, Italy, Russian Federation, and Switzerland) have not achieved interruption of measles and rubella transmission. In some of these countries major problems relate to political/societal will rather than technical or financial issues. In other EUR countries, for example Turkey and Ukraine, security and other concerns impede progress.
- Overall MCV1 immunization coverage in the region is stagnant (at 90-94%) or decreasing, and MCV2 coverage is 10% lower than MCV1.
- In some countries, groups of unimmunized persons (e.g. Roma, certain religious groups, and groups with certain philosophic beliefs) pose major programmatic challenges.
- Varied population/political situations within the region and even within certain countries necessitate development of tailored approaches to interrupt transmission.
- Case and outbreak investigation needs to be strengthened, as does the exchange of data among countries; In particular, rubella and CRS surveillance needs to be strengthened.

- Improved approaches need to be developed to identify and reach “new susceptible” populations such as adolescents and adults.

South East Asian Region (SEAR)

Status

With the establishment in 2013 of a measles elimination goal for 2020 and a rubella/CRS control target for the same date, all countries within SEAR have developed national plans of action to address measles and rubella/CRS either as a stand-alone plan or as part of National Health plans or National Immunization Program Plans. Despite this, at regional level, MCV1 coverage has stagnated at 84% since 2012. This figure hides inter-country variation: 6 (55%) of 11 countries sustained MCV1 coverage > 90% for the period 2010 to 2015. Except for Indonesia, India and Timor-Leste, all countries (with the exception of Thailand, which does not collect these data) reported over 80% of districts with MCV1 coverage > 80% in 2014. All countries have introduced MCV2 and regional MCV2 coverage was estimated at 59% in 2014. Nonetheless, measles continues to circulate widely in most countries of the region, primarily due to underutilization of measles vaccine. RCV is given in all SEAR countries with the exception of DPR Korea, India, and Indonesia. However, these three countries account for 87% of children < 1 year of age in the region.

Laboratory-supported case-based surveillance for all sporadic cases of measles is performed by all countries in the region except India and Indonesia. India and Indonesia limit the use of case-based surveillance to outbreaks, as the current incidence of measles is too high for the existing laboratory network to support case-based surveillance on an ongoing basis. CRS surveillance is routinely conducted in three countries: Bangladesh, Nepal and Sri Lanka. The RVC has recently been established with its first meeting having taken place in August 2016. Ten out of 11 countries have a National Verification Committee.

Significant challenges exist in surveillance for sample collection and transportation for laboratory confirmation of measles and rubella.

Conclusions and Recommendations

In spite of gradual increases in both MCV1 and MCV2 coverage, challenges to achieving measles elimination exist in SEAR. This is particularly true as India was estimated to have had 3.23 million children not receiving MCV1 in 2015 while Indonesia had 1.52 million. Apart from strengthening routine vaccination systems in the region (and particularly in these two countries) the following issues should be addressed:

- Closing the immunity gaps for measles and rubella in countries with large birth cohorts (India and Indonesia) through nationwide wide age range measles and rubella SIAs;
- Addressing gaps in surveillance for measles, rubella and CRS, including use of more sensitive case definitions. Only Maldives and Sri Lanka have achieved the desired non-measles-non-rubella discard rate of more than 2 per 100 000 population. In addition, most countries have difficulties with sample collection and transportation as well as inadequate linkage between case-based surveillance and laboratory data;
- Developing communication strategies to address issues with measles programming as well as care seeking behavior at various levels from community to policy makers;
- Developing guidelines to reduce nosocomial transmission of measles;
- Securing adequate MR supply to enable India and Indonesia to conduct nationwide SIAs and introduce MR in routine immunization.

If accelerated progress can be made in India and Indonesia and if these two countries close the population immunity gap for measles and rubella by 2018, the region has the possibility of achieving the

regional goal of eliminating measles by 2020; however, aggressive and innovative approaches are required.

Western Pacific Region (WPR)

Status

WPR set the goal of achieving measles elimination by 2012. Although it has a goal to eliminate rubella and prevent CRS, there is currently no target year associated with this goal.

In the region, 34 (92%) of 37 countries, (i.e., all except the Lao People's Democratic Republic, Solomon Islands and Vanuatu) have two doses of MCV in their routine immunization schedules and as of 2016 all countries and areas routinely provide at least one dose of RCV. Since 2009, both MCV1 and MCV2 coverage have been over 90% at regional level but variation exists between and within countries for which data are available, with only 33% of countries having both MCV1 >90% nationally and >80% in all districts. However, district-level data are not available in three countries: Fiji, Japan and New Zealand.

WPR's RVC was first convened in 2012, held annual meetings in 2013, 2014 and 2015 (i.e., four to date) and is scheduled to hold a fifth meeting in September 2016. As of end-2015, 7 countries and areas (Australia, Brunei Darussalam, Cambodia, Japan, Macao SAR (China), Mongolia and the Republic of Korea) have been verified as having interrupted endemic transmission of measles for more than 36 months, as determined by the RVC. The historic lowest regional measles incidence was experienced in 2012. From 2013, resurgence of endemic transmission occurred in China and the Philippines and large scale outbreaks followed importations in the Federated States of Micronesia, Malaysia, Mongolia, New Zealand, Papua New Guinea, Solomon Islands, and Viet Nam. Recent outbreaks of measles have occurred primarily among unvaccinated children less than 5 years of age (especially among those too young to be eligible for their first dose of MCV) and adolescents and young adults.

Although measles case-based surveillance is functioning in all countries/areas, rubella case based surveillance is less wide spread. CRS surveillance is being rolled out at sentinel sites in some countries (e.g., Papua New Guinea, and Viet Nam).

WPR provides an example of how a focus on measles elimination can improve coverage for some vaccines included in the country's recommended vaccination schedule. In China, a pilot project looking to assess the feasibility of measles elimination included a school entry check to make sure that children were vaccinated against measles. This was expanded to include a check to verify that children were up to date with all vaccines recommended by China's EPI. This system was then further expanded to other provinces in China. A graph depicting the impact of this school check on children's vaccination status is found below, as an inset box under Strategy 2, page 54.

Conclusions and Recommendations

WPR has all the ingredients to succeed in eliminating measles and rubella: high reported MCV1 and MCV2 coverage, high reported coverage with MCV delivered through SIAs, good case based and laboratory-supported surveillance and strong support of the RVC. However, some issues remain to be addressed:

- Resurgence of endemic transmission has occurred in countries with the largest populations in the Region: China, Philippines, Viet Nam and Malaysia;
- Reliance on "reported coverage" over measuring population immunity and thus underestimating the true number of susceptible individuals;
- Not routinely disaggregating coverage to lower administrative levels;

- Frequently leaving organization of follow up until too late, and not targeting a wide enough age group when SIAs are conducted;
- SIAs in priority countries (e.g. Lao PDR, Philippines, Viet Nam) often planned, prepared and implemented without effective strategies to identify and vaccinate children who had been missed and unvaccinated in the routine immunization program and/or previous SIAs, resulting in repeatedly missing the same children;
- Not systematically pursuing case- and laboratory based surveillance systems for early case detection and detailed analysis of outbreaks, although this is improving in China;
- Increased infection and transmission of measles virus among people outside the target age range of current immunization strategies (i.e., infants aged ≤ 8 months, adolescents and adults);
- In countries with large populations (e.g. China, Philippines, Viet Nam), the need to adjust the SIA target age groups to provincial age-specific attack rates;
- In contrast to polio, the lack of a major donor to the program and, with rapid economic development, the ability of fewer and fewer countries to avail themselves of Gavi funding;
- The lack of full implementation of infection control measures to prevent nosocomial transmission of measles when outbreaks occur;
- De-centralization and lack of commitment to the regional goal of elimination at the state or provincial level, particularly in priority countries such as China, the Philippines and Viet Nam.

The region is currently revising its *Regional Strategies & Plan of Action* and it is expected that the revised version will address these challenges.

SECTION 5. CORE STRATEGIES, BUILDING ON THE POLIO TRANSITION, GOVERNANCE AND RESOURCE MOBILIZATION

Strategy 1. Monitor disease using effective surveillance and evaluate programmatic efforts to ensure progress.

Background

Surveillance data are critical to guiding measles and rubella control and eradication efforts. Surveillance enables the establishment of burden of disease and mortality, and thus plays an important role in advocacy for and prioritization of activities targeting measles and rubella. Measles cases detected by surveillance identify un- or under-vaccinated populations, highlighting geographic areas or sub-populations in which vaccination programs overall – not only those targeting measles and rubella – require further support. Surveillance measures the best outcome indicator of disease control and eradication programs: disease incidence.

Well-done outbreak investigations are an important aspect of surveillance. Such investigations are invaluable to allow understanding of who is giving disease to whom. This information is critical to formulating effective vaccine strategy. For example, if, in families with multiple measles cases, the first case in the family is commonly found in a school-aged child and the second case is found in an infant, we may understand that transmission is from the school child to the infant and that breaking the chain of transmission will require vaccinating the school-aged child, not only the infant. Well-done outbreak investigations can also provide information to be used for economic analyses of the societal impact of measles or rubella.

□

Investigation identifies unvaccinated Amish at heart of outbreak

In 2014, the United States of America experienced a large outbreak of 383 measles cases. Outbreak investigations allowed these cases to be identified as occurring predominantly among unvaccinated Amish communities in Ohio.

<http://www.cdc.gov/measles/cases-outbreaks.html> Accessed July 10 2016

□

Investigation shows role of Apostolic Sect in large Zimbabwean outbreak

In 2009-2010, Zimbabwe experienced a large outbreak of measles with more than 2,000 cases. Outbreak investigations showed that approximately 75% of the cases were from the Apostolic Sect. This Sect refuses immunization based on religious beliefs.

UNICEF, WHO. Measles Outbreak Response in Zimbabwe. A proposal to respond to and control the ongoing measles outbreak in Zimbabwe. Harare, 2010.

□

Investigation demonstrates nosocomial infection in 45% of measles cases in S. Korea outbreak

In 2007, South Korea experienced an outbreak of 180 confirmed cases of measles. Eighty-one (45%) cases resulted from nosocomial transmission at six hospitals.

Choi WS, Sniadack DH, Jee Y, Go UY, So JS, Cho H et al. Outbreak of Measles in the Republic of Korea, 2007: Importance of Nosocomial Transmission. *Journal of Infectious Diseases*. 2011 204 (Suppl 1): S483-S490.

For all of these reasons, the MTR considers improving the quality of surveillance and outbreak investigations for measles and rubella over the next five years to be of primary importance. Because of this primacy, this report presents findings and recommendations related to surveillance and outbreak investigation before those related to immunization strategies.

WHO recognizes three levels of measles control associated with different incidences of measles: control in highly endemic settings of more than 5 cases per million population; accelerated control and mortality reduction in endemic settings with fewer than 5 cases per million; near elimination and elimination settings where cases are sporadic and outbreaks very small, with less than 1 case per million. WHO recommends, that the attributes of measles and rubella surveillance should change as countries progress toward elimination. WHO has also recommended the use of measles and rubella surveillance indicators to describe the quality of the surveillance being conducted. The indicators currently in use by WHO Regions are generally similar, although not identical.

Progress and challenges

Case-based²³ surveillance for measles exists in 188 (97%) of 194 countries. However, the quality of case-based surveillance is highly variable and the percentage of cases investigated varies a great deal among and within countries. Eight of 12 core data elements recommended for measles case investigations are common among regions (see paragraph below for listing of 12 data elements). Of WHO Member States, 94% report data monthly to regional offices. However, at present, 88 (45%) of 194 countries do not report case-based data to WHO Headquarters. Furthermore, data on age, vaccination status, and final case classification are often incomplete. The current data reporting cycle results in at least a two-month lag of data availability at global level. All regions use indicators to evaluate the quality of surveillance, although these vary slightly from region to region.

Case-based surveillance for rubella exists in 189 (97%) of 194 countries. However, currently, the quality of case-based rubella surveillance cannot be assessed at the global level as data have not been officially requested from regions. Not unexpectedly, given the fact that a global focus on rubella is relatively recent, surveillance for rubella remains weaker than that for measles. Nonetheless, in 2015, 164 (85%) countries reported testing at least 1 specimen for rubella in the measles rubella lab network.

Global measles surveillance guidelines were developed in 2003.²⁴ These guidelines were updated with the publication of WHO's Framework for verification of elimination of measles and rubella which recommends collecting 12 core variables.²⁵ These variables are: name or identifiers; place of residence; place of infection (at least to district level); age (or date of birth); sex; date of rash onset; date of specimen collection; measles-rubella vaccination status; date of last measles/rubella or measles-mumps-rubella vaccination; date of notification; date of investigation; and travel history.

Integrating rubella and measles surveillance is recommended in the three WHO Regions with a rubella elimination goal (AMR, EUR, WPR), as well as in SEAR which has established a rubella/CRS control goal.²⁶ Surveillance and outbreak investigations are underpinned by the diagnostic services of the Global Measles and Rubella Laboratory Network (GMRLN). This network of 723 labs provides confirmation of suspected measles and rubella cases by serologic and molecular methods, as well as providing information on global genotype distribution and evidence of interruption of transmission of endemic genotypes. The data that it provides support verification of elimination of measles and rubella.

Measles and rubella surveillance has taken advantage of existing, polio-funded surveillance personnel. Globally, of support provided by international donors, approximately 80% of surveillance personnel

²³ Case-based surveillance refers to surveillance systems that collect information about each case at the individual level. Murray J, Cohen AL. Infectious Disease Surveillance, Chapter in International Encyclopaedia of Public Health. In press, to be published 2017.

²⁴ World Health Organization WHO- Recommended Surveillance Standard of Measles. (http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/measles_standards/en/, Accessed July 9 2016).

²⁵ World Health Organization. Framework for verifying elimination of measles and rubella. *Weekly Epidemiological Record*, 2014, 88(9):89–99.

²⁶ SEAR defines control as a 95% reduction in estimated rubella/CRS cases relative to 2008 estimates both nationally and for the region. World Health Organization. Regional Office for South-East Asia Region. Regional plan for measles elimination and rubella and congenital rubella syndrome control. 2014-2020. Available at http://www.searo.who.int/entity/immunization/documents/sear_mr_strategic_plan_2014_2020.pdf Accessed August 10 2016.

(including data managers, field surveillance staff and laboratory staff) are paid for by polio funds and the remaining 20% paid by a combination of US CDC, BMGF and Gavi funding.

Discussion

From 2001 – 2015, substantial gains were made in measles surveillance. During 2004–2011, the number of countries using case-based surveillance, increased from 120 (62%) to 182 (94%); by 2015 this had increased to 189 countries. Expansion in case-based surveillance has been supported by expansion in the GMRLN. The GMRLN is a highly proficient laboratory network with a strong emphasis on quality control. It provides timely and accurate surveillance data to national programs, and has successfully introduced molecular methods for detection of measles and rubella, and genotyping. Laboratory testing has also successfully been integrated with that for other VPDs, such as yellow fever and Japanese encephalitis. The global sequence databases established for measles and rubella provide models for data sharing.

Despite these successes, the global measles and rubella surveillance system now faces four types of challenges. The first is that the system, as it currently exists, has not yet met its full potential. The second is the need to expand the system in order to better inform and guide disease control and eradication efforts as well as advocacy for these. The third challenge is to ensure that data are used to the fullest extent possible. The final challenge is to ensure that funding is adequate to meet programmatic needs particularly in an environment where measles activities supported by GPEI will be reduced.

The sensitivity of surveillance is assessed using an indicator of at least two discarded measles cases/100,000 population annually. This indicator is based upon limited data derived largely from a 2004 study which recommended 1/100,000 population as a minimum standard against which to compare the sensitivity of measles surveillance.²⁷ In contrast, enhanced surveillance for all rash and fever illness in Campinas Brazil, (a setting with high vaccination coverage against both measles and rubella), found an incidence of 181/100,000 population aged < 40 years.²⁸ Whether the current indicator is sufficiently sensitive to assure surveillance systems would detect circulating measles, if present, is unclear and requires further validation.

Other challenges exist. The extent to which the private sector is incorporated into the surveillance network is highly variable. Despite the existence of alternative specimen collection methodologies, traditional venipuncture remains the most frequent methodology used to collect specimens for laboratory confirmation. Most importantly, there is limited evidence that surveillance and outbreak investigation data are locally-owned and used to improve program management and guide disease control strategy. In terms of rubella, most countries in regions with rubella/CRS control or elimination goals have not yet integrated rubella and measles surveillance.

Although case-based surveillance for measles is now very widespread, it does not capture critical aspects of measles disease, such as complications and death. Inadequate surveillance data force

²⁷ Harpaz R, Papania MJ. Can a Minimum Rate of Measles-like Illnesses Serve as a Standard for Evaluating Measles Surveillance? *Journal of Infectious Diseases*, 2004, 189(Suppl 1): S204-S209.

²⁸ de Moraes JC, Toscano CM, de Barros EN, Kemp B, Lievano F, Jacobson S et al. Etiologies of rash and fever illnesses in Campinas, Brazil. *Journal of Infectious Diseases*, 2011; Sep 1; 204(Suppl 2):S627-S636.

estimates of disease burden and death to be mathematically modelled rather than being derived from real data. This limits the credibility and the value for advocacy of burden data.

The relatively sparse data collected during outbreaks do not permit a good understanding of who is transmitting measles to whom, thus limiting the extent to which outbreak investigations can guide strategy. These data are also too sparse to form the basis for such powerful advocacy tools as studies of the economic burden of an outbreak.

Enhancing surveillance will require investing more resources. However, even in its current state, the surveillance program has recently suffered serious financial setbacks linked to the decreased funding available to the M&RI, historically the major funder of measles and rubella surveillance networks. Networks are further threatened because they depend heavily on polio-funded staff and infrastructure. Funding for GPEI will decrease as of January 2017; unless polio assets are transitioned, existing measles and rubella surveillance networks will be seriously impacted. This is an urgent problem needing to be addressed.

Recommendations

- A top priority for achieving the goals of the *Measles Rubella Strategic Plan* is to enhance integrated case-based, laboratory-supported surveillance for measles and rubella. All countries must implement case-based surveillance for measles and rubella, and report case information to the WHO Regional Office on a weekly basis.
- A working group on surveillance and outbreak investigation and response should be developed at global level; this group should also provide guidance on linking surveillance findings with programmatic changes.
- Protocols should be updated or, when necessary, developed, to guide:
 - how to conduct outbreak investigations including: critical data to be collected; criteria for laboratory confirmation, guidelines for analysis, interpretation of analysis results, and presentation of the data (see Strategy 3 below);
 - setting up and strengthening surveillance systems to detect and investigate cases of rash illness and fever which could be measles or rubella, analyze the data, and interpret and disseminate the results of analysis for action and policy. For example, analysis should identify who is transmitting disease to whom, the role of failure to vaccinate versus vaccine failure, and in what settings exposure is occurring; and
 - selecting a representative subset of cases to be studied in-depth in settings of very high transmission where it may not be feasible to examine all cases in such detail.
- Sera collected to investigate cases of rash illness with fever to diagnose measles should be tested for rubella if found to be negative for measles, or tested for both measles and rubella at the same time. The results of laboratory testing should routinely be fed back to the original health care provider and the caregiver.
- Training materials should be developed based on existing experience for use at global, regional and country levels to design and improve systems to collect surveillance data, as well as to understand the underlying reasons that cases are occurring and disseminate results to all levels of the system.
- It is critical that there be country and local level ownership and use of surveillance and outbreak data for program improvement and advocacy.
- Countries need to dedicate resources for surveillance and partners need to supplement resources as needed, including resources for staffing, laboratory support, training, and other operational costs. Countries eligible for funding from Gavi should consider using Health System and Immunization Strengthening (HSIS) funding to support the surveillance infrastructure. Where appropriate, measles

and rubella surveillance systems should look for opportunities to also support surveillance for other diseases, for example dengue or yellow fever.

- Countries should take advantage of opportunities from the IHR review and national implementation of WHO evaluation of core capacities and lab surveillance strengthening to strengthen surveillance for measles and rubella.
- CRS surveillance, either sentinel or national level, should be implemented, especially in countries using MR.
- As the GPEI winds down, at a minimum the current level of measles and rubella surveillance should be maintained. Wherever possible, the polio transition should be capitalized on to further strengthen measles and rubella surveillance, as well as surveillance for other VPDs.
- The current measures to evaluate the quality of surveillance systems should be reviewed. Specifically, efforts should be made to determine if the indicator “occurrence of 2 cases of rash illness with fever per 100,000 children per year shown not to be measles or rubella” is adequate to say that measles would be detected if present in a given country.
- Both in outbreak investigations as well as in routine surveillance, all cases should be classified as preventable or non-preventable. A preventable case represents a program failure, i.e. a person who should have been vaccinated but was not. A non-preventable case is one for whom the current strategy does not offer direct protection. This represents vaccine failures in persons vaccinated according to schedule, persons with contraindications to vaccination, persons for whom vaccine is not indicated, and potentially other groups. Remedial actions need to be tailored depending on the distribution of cases in this classification. For example, remedial action for preventable cases would be to improve coverage in groups with these same characteristics. Detailed case investigation becomes ever more important as case counts are driven down. Persons of unknown vaccine status should be considered unvaccinated and thus preventable cases.

Strategy 2. Achieve and maintain high levels of population immunity by providing high vaccination coverage with two doses of measles- and rubella-containing vaccines.

Background

The extremely infectious nature of measles mandates very high levels of population immunity, generally considered to be 92 – 95 % in order to assure transmission²⁹ is stopped. Such levels of population immunity require delivery of two doses of MCV. Measles and rubella vaccines are routinely administered in the same syringe as MR. Current WHO policy is that two doses of vaccine can be administered through the routine immunization system, which is the preferred approach, or one dose can be administered through the routine immunization system while the second is administered through SIAs. Target age groups for SIAs are selected based upon the age distribution of susceptibility to measles in the population.

Progress and challenges

Globally, coverage with MCV1 has largely stagnated since 2008 (Figure 3). This figure hides heterogeneity in administrative MCV1 coverage among and within WHO regions, as well as within large countries such as China and India. Between 2010 and 2015, three regions sustained MCV1 above 90% (AMR, EUR and WPR), one maintained coverage between 80% and 90% (SEAR), and two regions maintained coverage below 80% (AFR and EMR). In 2015, 119(61%) of 194 Member States had achieved

²⁹ Orenstein WA, Gay NJ. The Theory of Measles Elimination: Implications for the Design of Elimination Strategies. *Journal of Infectious Diseases.* (, 2004), 189(Suppl 1):S27-S35.

Measles Rubella Midterm Review Report

the $\geq 90\%$ MCV1 national coverage target. By 2015, MCV2 was offered in 160(82%) of 194 Member States, up from 136 (70%) in 2010. Global coverage with MCV2 has continued to rise from 40% in 2010 to 61% in 2015.

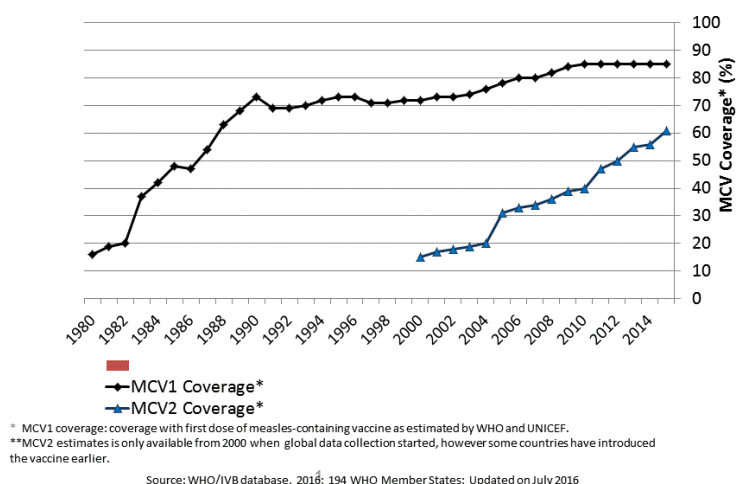


Figure 3. Coverage with first dose of measles-containing vaccine (MCV1) and second-dose of measles-containing vaccine (MCV2) as estimated by WHO and UNICEF, 1980 - 2015.

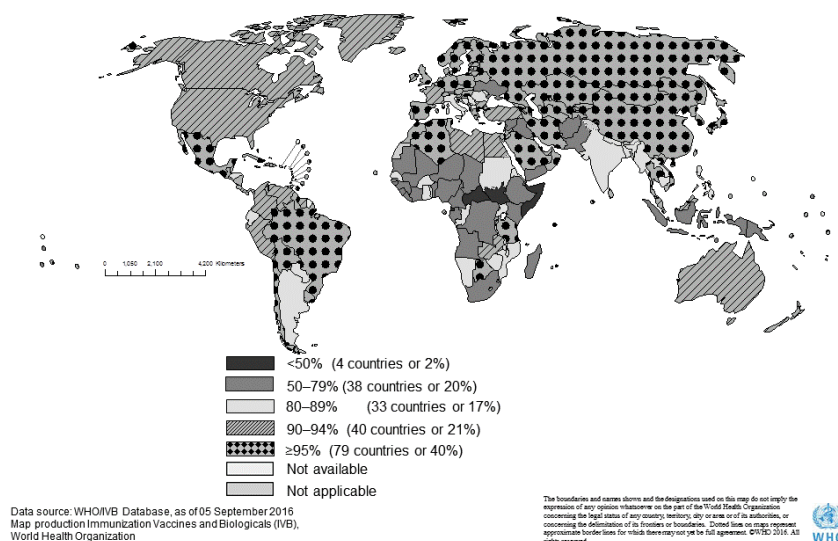


Figure 4. Immunization coverage (%) with first dose of measles-containing vaccines in infants per country, 2015

Measles Rubella Midterm Review Report

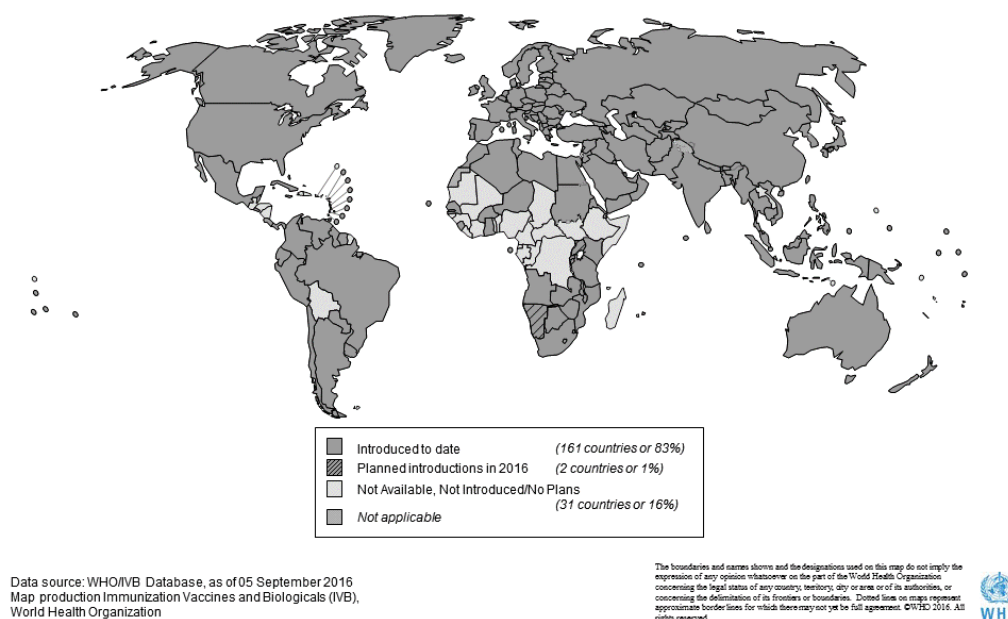


Figure 5. Countries that have introduced a second dose of measles-containing vaccine in the routine immunization system and those that plan to do so in 2016. Data as of September 2016

In many countries, the routine immunization system has been bolstered by SIAs. However, among 34 countries that conducted SIAs between 2012 and 2014 and that conducted a coverage evaluation survey of the SIA, less than half (16 Member States) were able to reach the target of 95% national coverage. At times, SIAs have also been delayed due to funding gaps.

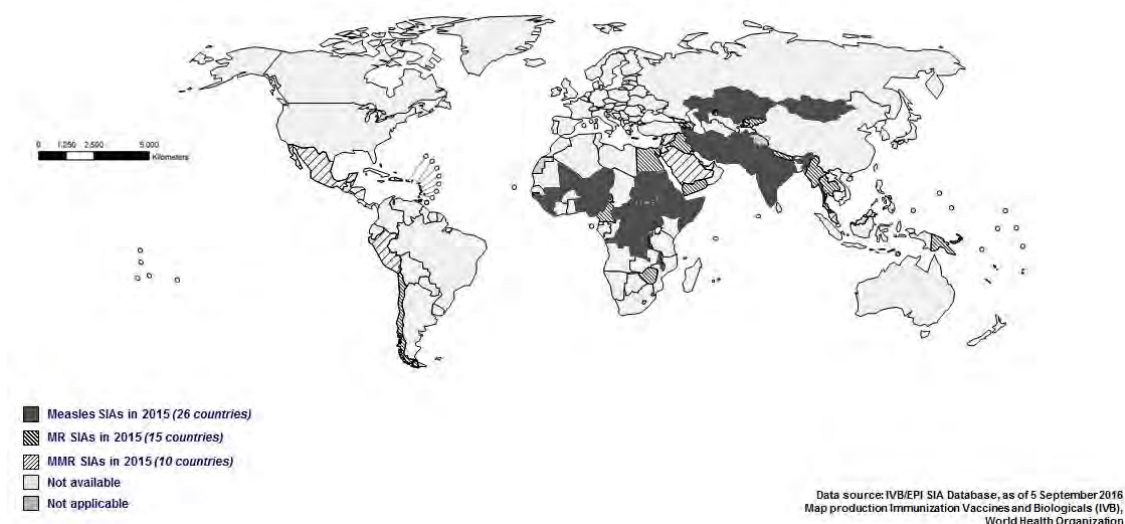


Figure 6. Measles, Measles-Rubella, or Measles-Mumps-Rubella SIAs conducted in 2015

Since 2012 (inclusive), 18 countries have introduced rubella containing vaccine.. From 2012 to 2014, global coverage with RCV rose from 42% to 46%.

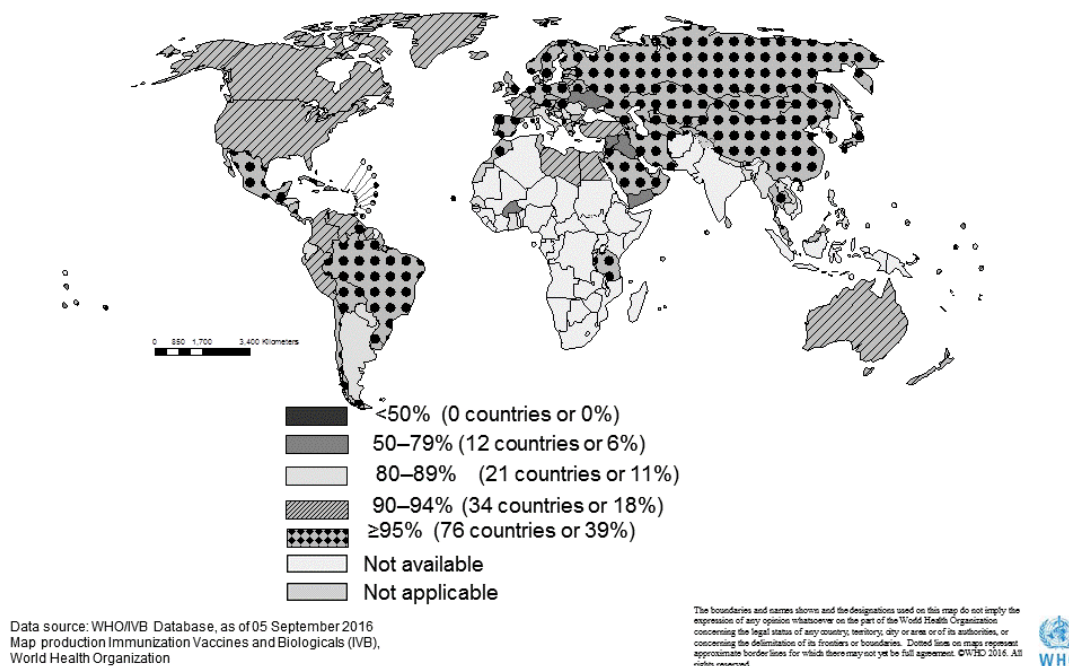


Figure 7. Immunization coverage with rubella-containing vaccines in infants, 2015

The Democratic Republic of the Congo’s experience: Poor MCV1 coverage and delayed SIAs lead to outbreak

During 2004 – 2010, national MCV1 coverage in the Democratic Republic of the Congo (DRC) increased from 57% to 73%. During the same period, the country conducted phased SIAs, at times with coverage < 95%. In 2010, SIAs in 5 of 11 provinces were not implemented as planned resulting in a prolonged interval between SIAs. In addition, a birth cohort was missed for vaccination in one province. A massive measles resurgence in DRC began in 2010 with 4,250 confirmed measles cases reported in 2010-2011. An investigation concluded that the outbreak was caused by an accumulation of unvaccinated, measles-susceptible children due to low MCV1 coverage and suboptimal SIA implementation.

Scobie HM, Ilunga BK, Mulumba A, Shidi C, Coulibaly T, Obama R et al. Antecedent causes of a measles resurgence in the Democratic Republic of the Congo. *Pan African Medical Journal*. 2015;21:30 doi:10.11604/pamj.2015.21.30.6335

Since 2012 (inclusive), eighteen countries have introduced rubella containing vaccine (RCV). From 2012 to 2015, global coverage with RCV rose from 42% to 46%.

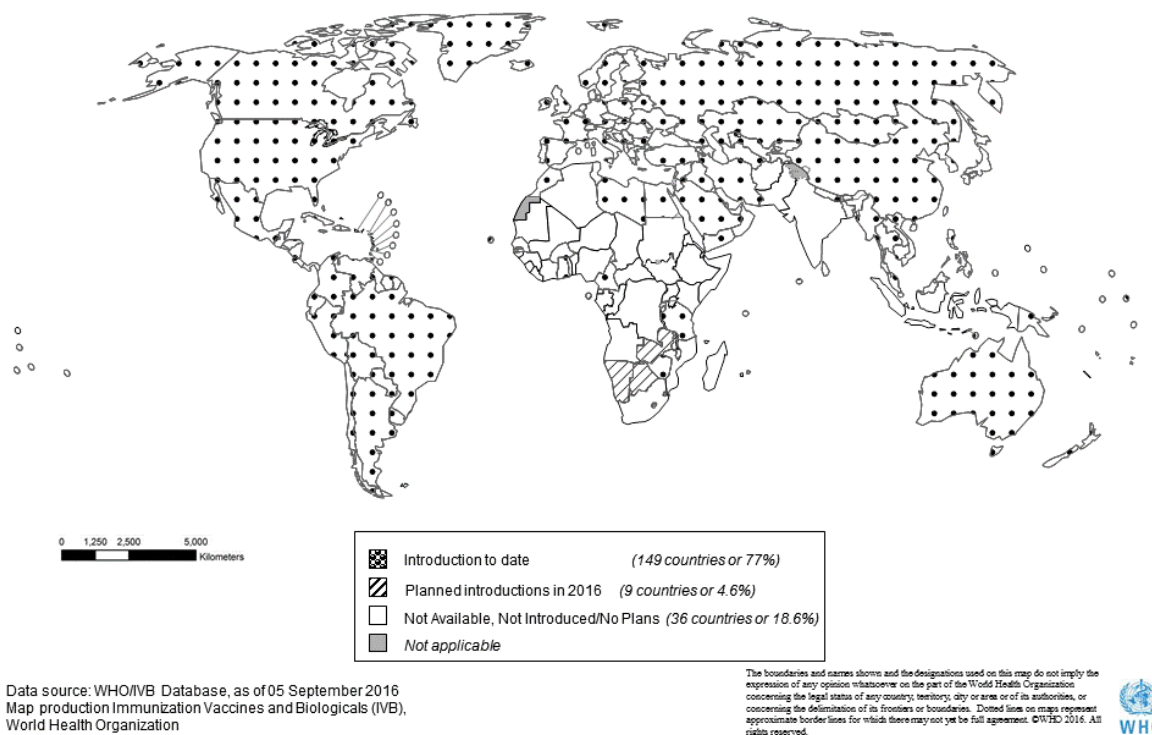


Figure 8. Countries that have introduced rubella-containing vaccine into the national program and those that plan to introduce 2016-2017. Data as of September 2016

□ **Kenya's experience: SIA delayed to allow concurrent distribution of bed nets leads to outbreak**

In 2002, Kenya conducted a nationwide, wide-age-range measles SIA resulting in a > 99% reduction in reported measles deaths. A follow-up measles SIA was initially scheduled for July 2005, but was delayed until 2006 following a decision to distribute insecticide treated bed nets concurrently with administering measles vaccine, as funding needed to be mobilized for the bed nets. After the introduction of measles virus in Sept. 2005, a large outbreak with 2544 reported measles cases during Sept. 2005 – May 2007 and 24 measles deaths occurred. This outbreak was attributed to the accumulation of children susceptible to measles due to the delayed SIA.

Centers for Disease Control and Prevention. Progress in Measles Control – Kenya 2002 – 2007. *Morbidity and Mortality Weekly Report*, 2007, 56(37); 56: 969-972.

Discussion

After substantial gains in the first decade of the century, increases in coverage with MCV1 have slowed. Gavi funding for RCV introduction has facilitated progress in rubella introduction in Gavi-eligible

countries which has, in turn, raised global rubella coverage. Nonetheless, in 2014 less than half of the global birth cohort was vaccinated against rubella.

Review of country-specific measles incidence and MCV1 coverage shows a strong link between high quality routine immunization programs (assuming reliable coverage reporting) and sustained high levels of measles control.³⁰ A strong routine immunization program allows timely delivery of MCV1 and MCV2 as well as the full range of other immunizations to the entire birth cohort. Conversely, the very high levels of coverage required to stop measles transmission can motivate identification of and attention to unvaccinated populations and missed opportunities for vaccination, which can benefit coverage of all vaccines and promote equity. For these reasons, and most critically, the measles and rubella control and eradication program must be fully integrated into the immunization program at every level – global, regional, national and local.

□

Measles SIAs and Gavi funds as catalysts for improving injections safety in Africa

‘In 2000, reuse of disposable syringes and inadequately sterilized syringes resulted in 39% of all infections being unsafe...In 19 (49%) of 39 countries, the measles program catalyzed the introduction of injection safety equipment, including (auto disable) AD syringes and safety boxes, training, and procurement of safety equipment during SIAs. Gavi was catalytic through financial support in 14 countries (36%) for including safe injection equipment in routine immunization. Additionally, Gavi funded 21 countries that had already introduced AD syringes in their national program. The measles mortality reduction program and Gavi complemented each other in improving injection safety. All countries continued with AD syringes for immunization after measles catch –up SIAs and Gavi funding ended’

Hoekstra EJ, van den Ent MMVX, Deo H, Salovaara A. Measles supplementary immunization activities and Gavi funds as catalysts for improving injection safety in Africa. *Journal of Infectious Diseases*, 2011;204 (Suppl 1): S190 –S197.

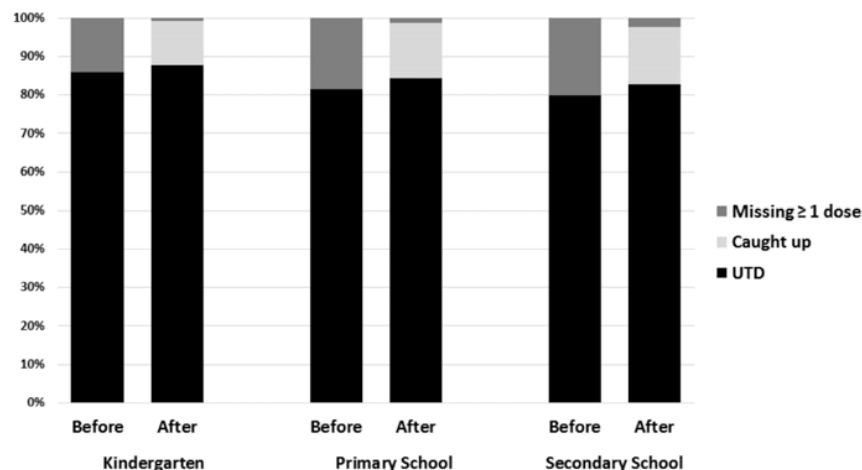
³⁰ http://www.who.int/immunization/monitoring_surveillance/data/en/ Accessed July 20, 2016

□

School entry vaccination checks in China increase coverage for all vaccines

As part of a pilot project to look at the feasibility of measles elimination in China, the country implemented school entry checks for measles vaccination. Other vaccines were also checked. The school entry check has been expanded within China. A recent study of the impact of school entry checks in Ninyang County, Shandong Province showed how they detected students that had been missed through routine services and increased coverage for all vaccines.

Impact of School Entry Vaccination Record Check, Ningyang County, Shandong Province, 2015



Vaccines that are needed for the child to be considered up-to-date (UTD) and that are checked as part of the school-entry check:
 Kindergarten (age 3 yr): 1 BCG; 3 HepB; 1 or 2 HepA (depending on the vaccine); 3 DTaP; 3 tOPV; 2 JEV; 2 M/RCV; and meningococcal vaccine.
 Primary (elementary school) and secondary (middle and high school): same as kindergarten, but 4 doses of tOPV instead of 3 doses

YIN Xiu-wang, et al. *Chinese Journal of Vaccines and Immunization* 2016;13(5): in press

□

Measles elimination plays a key role in building the National Immunization Program of the United States of America

'In 1966....the Centers for Disease Control and Prevention began an effort to eliminate measles within the United States....With measles elimination as the primary driver, fundamental components of today's immunization program were built that affected not only measles, but all of the vaccines and vaccine-preventable diseases of childhood. Some of the major contributions were the enactment and enforcement of immunization requirements for school attendance in all 50 states, enactment of an entitlement program for vaccine purchase, the Vaccines for Children Program, support for health services research to determine reasons for non-immunization and interventions to improve coverage, development of standards for immunization practices and the measurement system for immunization coverage in all 50 states and 28 major urban areas. Key lessons have been: (1) the program must rest on a sound base of vaccine science and health services science; (2) having a limited number of measurable goals allows program focus, but consider strategies that have crosscutting impact; (3) accountability is critical to program performance at all levels – state, local and individual practice; and (4) establishing and maintaining political support is essential.'

Orenstein WA. The role of measles elimination in development of a national immunization program, *Pediatric Infectious Disease Journal*, .2006, Dec; 25(12): 1093 –1 101.

Both the epidemiology of measles and the challenges faced by programs vary within regions and, in some settings, within countries. An increasing problem in some settings has been the rising incidence of measles outside the target age group of current immunization strategies (i.e., infants aged < 8 months, adolescents and adults). Four of the six WHO regions have recognized the need to tailor recommendations for measles control to the local setting by grouping countries into categories, and making recommendations by category. Developing globally standardized criteria for grouping countries as well as globally standardized recommendations by group (neither of which currently exists) would recognize the reality of differing program performance and allow specific but globally-standardized guidance to be offered to countries. This type of grouping would also allow a more nuanced description of the world's progress with regard to measles and rubella eradication than is currently possible. The review team has selected country examples from each WHO Region to illustrate successful, fragile, and seriously-challenged programs. Program performance is reflected in disease incidence and age and vaccination status of measles cases. More information on each region and selected countries is found in the Appendix (available for the web-based report).

An important programmatic consideration is how best to achieve very high two-dose coverage. Approaches may include school entry checks for measles and rubella (as well as other) vaccines, provider-based record review and catch-up vaccination, and SIAs. However, the challenge of reaching consistently high SIA coverage in the face of funding gaps and increasing complacency with falling disease incidence is underlined by the percentage of SIAs with measured coverage less than 95%.

The traditional emphasis placed on vaccination coverage as opposed to incidence should be reconsidered. Conceptually, incidence is an outcome indicator, whereas coverage is an intermediate indicator. In addition, administrative coverage is plagued by unreliable denominator data while

precisely measuring coverage at the very high levels of coverage required to stop transmission is also technically difficult. Nonetheless, to the extent possible, coverage should be validated, and differences in coverage between MCV1 and MCV2 should be monitored. The most effective way of achieving and maintaining very high dose coverage is through the routine immunization system.

Recommendations

- Measles and rubella control and elimination activities at national level should be located within the overall immunization program.
- The incidence of measles and rubella and coverage with measles and rubella vaccines should be considered among the primary indicators of immunization system performance.
- Two doses of MCV or MRCV delivered through ongoing services is the standard for all national immunization programs. Preventive SIAs should be conducted on a regular basis, if routine two dose coverage is insufficient to achieve and maintain high population immunity. In certain circumstances, one-time SIAs may need to be conducted to close existing immunity gaps in the population, for example immunity gaps among adults.
- Efforts to enhance measles and rubella prevention should take into account the importance of strengthening the overall immunization delivery system. For example,
 - delivery of MCV2 can be used as a platform to deliver other health interventions (i.e., helping to establish a second-year-of-life platform);
 - in planning SIAs, the enumeration of high-risk communities can be focused to also improve delivery of routine immunization services to these same populations.
- A standardized method to classify countries based on their level of disease control and likelihood of achieving and sustaining achievement of measles and rubella elimination goals should be developed. The major purpose of such a classification is to tailor outbreak response and surveillance strategies appropriately. Large countries in which measles epidemiology is not uniform should adjust their measles control and elimination strategies to subnational settings.
- The current approach for determining the target age range for M and MR SIAs should be re-evaluated. This includes the potential for developing new guidelines based on more detailed analysis (including mathematical modelling) of sub-national coverage/disease incidence data to guide vaccination strategies.
- Approval of financial support from international partners for preventive SIAs should be conditional on country commitment to meet minimum standards of readiness as articulated in the SIA readiness checklist.
- Non-Gavi-eligible countries should take advantage of strategies being developed by WHO, Gavi and UNICEF to address financing of vaccines in these settings.
- Efforts should be made to determine key reservoirs for measles and rubella that have proven to be exporting disease and take remedial action to terminate transmission in those areas/populations.
- The accuracy, completeness and timeliness of administrative coverage data must be improved to increase their usefulness both at national and sub-national level.
- Use of the district level program risk assessment tool, which takes into account reported or evaluated coverage, surveillance data, and program performance data to identify areas requiring special efforts, should be encouraged.
- All countries should institute a school entry check for immunization, including vaccination against measles and rubella as well as against other VPDs. Vaccination should be provided to children who have not received vaccine.

- Every opportunity should be taken to vaccinate people not adequately vaccinated, particularly those under 15 years of age. Policies which prohibit use of vaccine in children >1 year of age, older children and teenagers should be changed to allow these individuals to be vaccinated.
- Quality of SIAs should be systematically and rapidly assessed. In the case of underperformance, remedial action should be taken immediately. Campaign planning and budgeting should always include "mopping-up" activities in poor performing areas.
- The current criterion recommended by WHO for introduction of MCV2 into the routine schedule, i.e., WHO/UNICEF estimates of MCV1 coverage greater or equal to 80% for three consecutive years,³¹ should be re-assessed.
- In principle, all doses of vaccine delivered (including through SIAs) should be documented, for example in the home-based record and, in those countries introducing computerized record systems, in the patient's electronic record.

Strategy 3. Develop and maintain outbreak preparedness, respond rapidly to outbreaks and manage cases

Background

Outbreaks provide important opportunities to gather data on who is susceptible to measles or rubella, and how this susceptibility may reflect program weaknesses. Outbreak investigations allow determination of whether the outbreak is due to vaccine failure, or failure to vaccinate. In addition, data gathered in outbreaks (e.g., deaths, economic costs) can be critical for political advocacy.

Prior to 2008, outbreak response immunization (ORI) was discouraged in lower and lower middle income countries.³² Global outbreak response guidelines were modified in 2009 to facilitate outbreak response, in recognition of the fact that outbreaks in certain settings last for many months and that the length of these outbreaks provides opportunities for morbidity and mortality reduction through vaccination response.³³ Global rubella outbreak investigation and response guidelines have recently been published by WHO.³⁴

Progress and challenges

At present, global guidelines for measles and rubella outbreak investigations exist, but the measles guidelines are basic and do not provide guidance on collecting much of the information that is needed both to understand disease transmission patterns and for advocacy (see Strategy 1). A specific measles outbreak-related challenge is to develop an appropriate algorithm which allows for adequate laboratory testing without overwhelming the laboratory with samples.

³¹World Health Organization. Measles vaccines: WHO position paper. *Weekly Epidemiological Record*, 2009,84:349-360.

³²Aylward RB, Clements J, Olive JM. The impact of immunization control activities on measles outbreaks in middle and low income countries. *International Journal of Epidemiology*, 1997, 26 (3):662-669.

³³World Health Organization. *Response to measles outbreaks in measles mortality reduction settings*. Geneva, World Health Organization, 2009, i-36 (WHO/IVB/09.03, http://apps.who.int/iris/bitstream/10665/70047/1/WHO_IVB_09.03_eng.pdf accessed 8 August 2016).

³⁴World Health Organization. *Introducing rubella vaccine into national immunization programs. A step-by-step guide*. WHO/IVB/15.07 Geneva, World Health Organization, 2015 (WHO/IVB/15.07, http://apps.who.int/iris/bitstream/10665/184174/1/9789241549370_eng.pdf).

Since 2013, a Gavi-funded measles outbreak response fund of USD 10 million annually has existed, administered by the M&RI through WHO. This fund has recently become available for rubella outbreaks as well. The goal of this funding is to enable countries experiencing measles or rubella outbreaks to rapidly respond to these while they are still relatively small and localized, thus preventing them from developing into large and widespread outbreaks. Funding is restricted to Gavi-eligible countries. The age groups that can be targeted may also be restricted. Once the M&RI receives a completed request for funding for ORI, funds can be disbursed to the national government within 48 hours. However, vaccination response within country may be slowed by the need to decide what geographic areas and age groups to target for vaccination. No external funding for ORI is available for non-Gavi eligible countries.

Discussion

The existence of measles and rubella outbreak investigation and response guidelines as well as funding for measles and rubella ORI in Gavi-eligible countries reflects progress in outbreak investigation and control. However, the full potential of outbreak investigations to inform and advocate for the program has not been met. Outbreaks result in increased morbidity and mortality as well as disruptions of and expenses to health care services. Outbreaks should be used as opportunities to sensitize policy makers and the public to the importance of preventing, rather than responding to, outbreaks. From a technical perspective, measles outbreak investigation guidelines need to be updated, should provide guidance on what outbreaks to investigate and how, and should reinvigorate efforts to prevent nosocomial transmission. For example, investigation of outbreaks should attempt to determine in families or household settings where there is more than one case, the characteristics of the index case (e.g., age, vaccination status, attendance at a school, prior visit to a healthcare setting, etc.).

Experience with the Gavi ORI fund has seen some countries delay response to measles outbreaks for months, both while preparing a request for funding and after receiving vaccine. The reasons for such delays can be complex, including the political ramifications of declaring an outbreak, lack of awareness of how to apply for ORI funding, and uncertainty as to who to vaccinate. Prompt response would diminish the mortality and morbidity associated with the outbreak, but requires strong country ownership.

The ORI fund currently available is also limited because it cannot be used for non-Gavi countries (including those that have recently graduated). Although the M&RI responds rapidly to requests for ORI funding for Gavi-eligible countries, the time-to-request as counted from the beginning of the outbreak may be months. In addition, once funding has been released it may take months before ORI occurs, resulting in the opportunity for the outbreak to spread widely and decreasing the extent to which ORI can mitigate morbidity and mortality associated with the outbreak. Furthermore, although the ORI fund is substantial, some populous countries with poor measles control (e.g., DRC and Pakistan) have had financial requirements which surpass the magnitude of available funding.

The need for outbreak response may depend upon the background immunity in the population –(i.e., in countries with very high background immunity outbreaks may be expected to die out, whereas in countries with low background immunity outbreaks may continue for many months). Recommendations regarding response may vary accordingly.

Recommendations

- Emphasis should be placed on prevention of outbreaks through monitoring of risk status, for example through the use of risk assessment tools, and increased attention to vaccination in high risk settings.
- All measles outbreaks should be promptly investigated and used to develop a susceptibility profile of the population to better inform measles control and elimination strategies, including outbreak prevention and response immunization.
- Countries should develop national measles outbreak preparedness and response plans and build national capacity to investigate and respond to such outbreaks. A clear definition of what constitutes a measles outbreak that can be used to prompt outbreak investigation and control measures is required. Country ownership with regards to rapidly investigating and responding to measles and rubella outbreaks should be encouraged.
- Based on existing experience, training materials should be developed for use at global, regional and country levels to perform outbreak investigations as well as to understand the underlying reasons that outbreaks are occurring and disseminate results of these investigations to all levels of the system. Protocols should guide critical data to be collected as well as guidelines for analysis, interpretation of analysis results, and presentation of the data (see Strategy 1 above).
- Guidance should be developed to allow countries to assess the economic burden of outbreaks. Information on the cost and disruptiveness of outbreaks, including the costs incurred in controlling outbreaks, should be collected to use as an advocacy tool and to encourage preventive action.
- There is need for global guidelines for outbreak investigation and response for elimination settings, including contact tracing and the identification of population immunity gaps.
- There must be adequate financial, human and laboratory resources to conduct adequate outbreak investigations. Gavi-eligible countries should consider using HSIS funds for this.
- Financial resources should be urgently mobilized to support outbreak investigation and control in non-Gavi eligible countries. Countries should develop national Measles Outbreak Preparedness and Response Plans. Outbreak preparedness and response capacity should be assessed by RVCs or by regional immunization Technical Advisory Groups (RITAGs).
- When outbreaks are detected, in addition to investigation, countries should take steps to mitigate the outbreak through vaccination. The magnitude of the response should be based on the characteristics of the outbreak, the stage of measles control, and the category to which countries belong. The more rapid the response, the more likely it is to mitigate the impact of the outbreak.
- In countries that have introduced rubella-containing vaccines, outbreak immunization measures should be based on the susceptibility profile of the population, the groups affected, and the availability of vaccine.
- During and following a rubella outbreak, pregnant women should be registered and followed according to existing guidelines.
- When massive outbreaks occur, minimal information can be collected on all cases, but intensive investigations of a representative subset should be carried out to determine the underlying causes of the outbreak so that actions can be taken to prevent similar outbreaks in the future.

- When conducting case-based surveillance, at a minimum, twelve core³⁵ elements should be investigated for each case as well as a classification of whether or not the case is preventable. The outbreak investigation response should be tailored to the classification of countries.

Strategy 4. Communicate and engage to build public confidence and demand for immunization.

Background

Communication is critical to make populations aware of where, when and why they should be vaccinated – both routine immunization and SIAs. It is also critical to help policy makers and health workers understand why and how to support immunization programs. Communication is also critical to build and maintain public confidence in immunization. This is particularly the case in the wake of adverse events following immunization (AEFI) or other events that raise concerns about the safety of immunization.

Progress and challenges

The Gavi Secretariat has the strongest communications team for supporting all its immunization activities including measles and rubella. In addition, each of the five M&RI founding partners has communications specialists. However, with the exception of UNICEF which has hosted a communication specialist focusing on measles and rubella activities since 2013, these specialists handle a broad range of topics. In 2014, communication specialists from all M&RI core partner agencies developed a strategic communications plan for the M&RI. The objective of this plan was to support achievement of the 2015 and 2020 goals of the *Global Measles and Rubella Strategic Plan 2012-2020*.

The ARC focuses on social mobilization for immunization by mobilizing and training volunteers from national Red Cross and Red Crescent societies for house-to-house visits. However, financial constraints limit this service to approximately 500,000 children per country. Although house-to-house mobilization could be used to sensitize populations to the need for routine immunization as well as awareness of SIAs, a desire to optimize the impact of the limited funds available has led to a focus on SIAs and urban populations. A small, unpublished study comparing coverage achieved during an SIA in districts without house-to-house mobilization to that achieved in districts with house-to-house mobilization showed that the districts with house-to-house mobilization showed an increase of 6-12 percentage points in vaccination coverage. However, lack of funding has limited the ability of ARC to conduct larger studies on this topic.

UNICEF plays a lead role in communications. This includes channeling and/or adding resources to the UNICEF Communications for Immunization (C4I) initiative at country level to be used for measles and rubella immunization activities and technical assistance. However, there remains an emphasis on traditional approaches to social mobilization such as printed materials and television spots despite unpublished recent data indicating the success of less traditional methods, for example town criers.

³⁵ World Health Organization. Framework for verifying elimination of measles and rubella. *Weekly Epidemiological Record*, 2014, 88(9):89–100.

Relatively few communications messages specifically target rubella. Resources have not been adequate to target the multiple audiences implicated in immunization programs, such as politicians, public health leaders and workers, public and private healthcare providers and parents.

Discussion

Since 2012 there has been an increased emphasis on the importance of communications, as evidenced by the creation of a dedicated post in UNICEF and the development of a strategic communications plan. While many activities demonstrate dedication and creativity, the scope of these activities – in terms of numbers reached and breadth of focus – appears limited by resources. The ability to argue for more resources based on the impact of communications activities is limited by a lack of data; the ability to generate such data is, in turn, limited by lack of resources.

Communications teams need to have the resources to craft and test messages aimed at particular target audiences, such as politicians, public health leaders and workers, health care providers, and parents. In selecting media to reach target audiences, existing information on what media are most effective should be carefully considered. In keeping with the concept that measles and rubella immunization needs to remain firmly embedded in the routine immunization program, in communications the importance of immunizations overall should be emphasized with a particular focus on measles and rubella immunization.

Information on incidence, burden of mortality and vaccination coverage are critical. However, it is important not to overlook the role that anecdotes play in illustrating statistical data and capturing the attention of policy makers and the public. The mortality and morbidity as well as the disruption and expense associated with outbreaks provide opportunities to remind policy makers and the public of the importance of preventive vaccination.

Rubella and its sequelae remain poorly known in much of the world. As the implications of rubella infection are substantially different from those of measles infection, it is important to develop messages specifically focused on the importance of immunization against rubella.

Recommendations

- Increased resources are needed for communication to raise the visibility of VPDs and the importance of ongoing immunization services, with a focus on measles and rubella.
- Creating and promoting demand for immunization requires long term investment and should be an integral part of routine immunization strategy.
- Communication plans may target many different audiences (e.g., politicians, public health leaders and workers, healthcare providers, caregivers, etc.). Plans targeting each of these audiences should be developed and audience-specific messages developed and tested.
- Communication research science should be used to identify the most effective means of communication; these data should inform the communication strategies selected.
- Outbreaks of measles or rubella should be recognized as opportunities to promote the importance of immunization in preventing outbreaks, with particular focus on measles and rubella vaccination.
- Messages specific to rubella need to be developed, tested, and used.
- Data on measles incidence, including complications and deaths, as well as information on the costs associated with outbreaks, should be the focus of educating various audiences about the importance of preventing the illness. Data should be supplemented by stories of actual cases to

illustrate the statistical data. Collection of information on cases of CRS can also be a powerful advocacy tool.

- Outbreaks should be an opportunity to sensitize medical professionals about the risk of nosocomial transmission of infectious diseases and take proper preventive measures.
- In advocating for improved prevention of measles and rubella, it will be important to collect stories of how a focus on those diseases not only improved their control but also helped to enhance overall immunization and health systems (see Resource Mobilization Section below).

Communications plans should address hesitancy toward vaccination and building confidence in vaccines. This should include risk communication following publicized adverse events following immunization, and promotion of the safety of vaccines.

Strategy 5. Perform the research and development needed to support cost-effective operations and improve vaccination and diagnostic tools.

Background

Experience with smallpox and polio has shown the disease control gains that can be made by targeted and programmatically –driven research. Research can be critical to breaking through periods of program stagnation, particularly if it results in the dissolution of barriers limiting program performance.

Progress and challenges

Since 2005, six global meetings focused on measles and rubella research have been held, with the most recent in 2015. A further meeting to prioritize research topics is proposed for the fourth quarter of 2016. An independent survey of individuals working programmatically or in academia on measles and rubella control was conducted with the goal of identifying gaps in essential evidence and program barriers to achieving measles and rubella/CRS elimination; the results of this survey were endorsed by the SAGE in 2014. This survey indicated that the most important areas for research were considered to be developing novel ways to optimize vaccine delivery and assess vaccination coverage (Table 3).

To promote and advocate for measles and rubella research, the M&RI has established a Research and Innovation Working Group, chaired by CDC. Total funding available annually, primarily from CDC and BMGF, is approximately USD 1 million. At present, there is no standard approach to prioritizing research topics or to ensuring ongoing funding of research.

Measles Rubella Midterm Review Report

Research Topics	Status of progress as of July, 2016*
Global Measles and Rubella Research priorities for MR control and eradication identified at WHO meeting of experts held at CDC, and published in Vaccine (2012;30(32):4709-16	
Measles Epidemiology	
<i>Measles epidemiology in various settings in India</i>	*
<i>Causes of measles outbreaks in high vaccination coverage settings</i>	**
<i>Adult measles susceptibility in suboptimal vaccination coverage settings</i>	*
<i>Adult vaccination needed to reach and maintain elimination</i>	*
<i>Need for measles vaccination prior to 9 months of age</i>	**
<i>Measles susceptibility among HIV-infected adults</i>	**
Vaccine Development and Effectiveness, and Alternative Vaccine Delivery Methods	
<i>Measles vaccine effectiveness in densely-populated settings</i>	*
<i>Thermo-stable vaccines, alternative delivery methods (needle-free devices, aerosol, dry powder, microneedles)</i>	**
Surveillance and Laboratory Methods	
<i>Global distribution of measles virus genotypes</i>	***
<i>Rapid diagnostic tests to detect cases in the field</i>	**
<i>High throughput tests to accurately measure neutralizing antibodies</i>	*
<i>High resolution molecular sequencing methods</i>	**
<i>Assays to differentiate vaccine-acquired immunity and immunity from exposure to wild-type viruses</i>	*
Immunization Strategies	
<i>Second year of life strategies for increasing vaccination coverage</i>	**
<i>Strategies to maximize SIA coverage</i>	**
<i>Methods for monitoring vaccination coverage through routine and SIAs</i>	**
<i>Strategies for identifying, vaccinating nomadic populations, migrants, refugees</i>	**
<i>Communication messages and strategies that increase demand for vaccination in various settings</i>	*
<i>Strategies for outbreak response immunization activities</i>	*
Mathematical Modeling and Economic Analyses	
<i>Modeling progress toward measles eradication</i>	**
<i>Modeling approaches to estimate population size and susceptible density required to sustain transmission</i>	*
<i>Economic burden of measles outbreaks in low and middle income countries</i>	**
Rubella/CRS Control and Elimination	
<i>Epidemiology of rubella/CRS in settings with varying birth rates</i>	**
<i>Optimal methods and corresponding costs for CRS surveillance, in areas with weak health systems</i>	**
<i>Global distribution of rubella virus genotypes</i>	*
<i>Economic burden of rubella and CRS at global, regional and national levels</i>	***
SAGE MR Work Group prioritized 12 research topics by a survey of experts, and endorsed by SAGE in 2014	
<i>Strategies to increase coverage in difficult populations</i>	**
<i>Novel strategies to increase vaccine coverage</i>	**
<i>Strategies to address confidence gaps</i>	*
<i>Outbreaks in settings with high coverage</i>	*
<i>Optimal age of measles vaccination</i>	**
<i>Reasons for low confidence in vaccines</i>	**
<i>Outbreak response strategies</i>	*
<i>Strengthen routine immunization & surveillance</i>	**
<i>Susceptibility profiles to measles and rubella</i>	**
<i>Measures of vaccine coverage</i>	**
<i>Epidemiology & surveillance for rubella & CRS</i>	**
<i>Point of care diagnostics</i>	**

*not adequately being addressed, **somewhat being addressed, ***well addressed

Table 3. Measles and rubella research priorities and status of implementation

Discussion

The Research and Innovation Working Group has been instrumental in raising the profile of measles and rubella research, and promoting a coordinated approach to prioritization of research projects. Potentially ‘game-changing’ advances are in development, with the most critical likely to be administration of vaccine through microarray patches (MAPs) (also known as ‘microneedles’). This technology would allow non-medically trained personnel to administer vaccine, which would be of critical importance in countries with limited human resources. In addition, it would allow house-to-house administration of vaccine, potentially increasing coverage to levels high enough to achieve herd

immunity. Such innovations would enhance the likelihood of success in reaching regional elimination goals.

While research is often seen in terms of technology, equally important is operations research. Operations research can assist in appropriately guiding the implementation of basic strategies, and the tailoring of approaches to local contexts. Programmatic questions that should be addressed include the best ways of reaching hard-to-reach populations, how to enhance disease surveillance, and the best approaches to measuring vaccination coverage. At times, this research may be context-specific. Country-led research would benefit from further emphasis. Research targeting programmatic and, at times, country-specific challenges, as has been done in the polio program, is likely to yield the most programmatic gains and should be prioritized.

Progress has been made in exploring topics identified as priorities at previous measles and rubella research meetings (Table 3). However, measles and rubella research activities remain under-funded and without dedicated staff. Attempts to identify funding for research have focused on a small number of donors and could be expanded to a much broader group. Measles and rubella research is also a natural successor to the Polio Research Committee (PRC). Transitioning the PRC to measles and rubella research should be considered part of the overall polio transition.

Recommendations

- Programmatically-oriented operations research, in addition to technologically-oriented research such as the development of new vaccine delivery or antibody testing methods, should be used to determine how to best interrupt measles transmission. Such operations research should include achieving optimal uptake of vaccination in populations, which populations should be targeted for special immunization efforts, how to optimize surveillance systems, and the economic impact of disease.
- Sustained commitment to adequately funding measles and rubella research is required. An advocacy plan to secure funding for research should be developed.
- A working group focusing in a sustained fashion on advocating for, promoting, and prioritizing measles and rubella research, similar to the PRC, is critical. The natural home for this working group is WHO.
- Research should be conducted to determine the impact at the country level of measles and rubella control and elimination efforts on the overall immunization system.

- **Building on the Polio Transition**

- Background:

Pursuing the goal of poliomyelitis eradication has led to the commitment of vast human and financial resources. The *Polio Eradication and Endgame Strategic Plan (PEESP) 2013 – 2018* articulates 'Transition Planning' as its fourth Objective, stating that (governments should) "...ensure that the investments made to eradicate poliomyelitis contribute to future health goals, through a program of work to systematically document and transition the knowledge, lessons learned and assets of the Global Polio Eradication Initiative... and establishment of a comprehensive polio transition strategic plan by no later than end-2016".³⁶

Progress and challenges

A subcommittee of the GPEI has been tasked with Polio Legacy Transition Planning. This subcommittee has defined the three key components of polio legacy transition planning as:

- Maintaining and mainstreaming essential polio functions (e.g., immunization, surveillance);
- Sharing knowledge and lessons learned from GPEI to improve child health globally;
- Transitioning polio capacities, infrastructure and assets to support other public health priorities, where appropriate.

At present, more than 30,000 individuals comprise the internationally-supported GPEI workforce, while more than 700 laboratories form the Polio Laboratory Surveillance Network. In addition to performing their polio functions, these 30,000 individuals provide support to a broad array of immunization and health initiatives which will not phase out with GPEI. A survey of polio-funded staff done by the Boston Consulting Group indicated that approximately 46% of the staff's time was spent on polio eradication, 22% on routine immunization, 8% on measles elimination, rubella control and 4% on new vaccine introduction, and the remainder on a variety of other health initiatives (Figure 9)³⁷. Working toward polio eradication has taught the immunization community many lessons including how to access insecure and hard-to-reach areas, accountability, the importance of communications, how to optimize social mobilization and community engagement, how to achieve and maintain political commitment, and how to operate global disease surveillance networks. These lessons are relevant to a broad swathe of disease control initiatives.

³⁶The Global Polio Initiative. *Polio Eradication & Endgame Strategic Plan 2013-2018*. 2013, Geneva, World Health Organization (WHO/POLIO/13.02, <http://www.polioeradication.org/resourcelibrary/strategyandwork.aspx>, accessed 9 July 2016).

³⁷ Boston Consulting Group. Polio funded personnel's involvement in routine immunization and broader immunization goals. Final report, May 2015, 1-82.

Measles Rubella Midterm Review Report

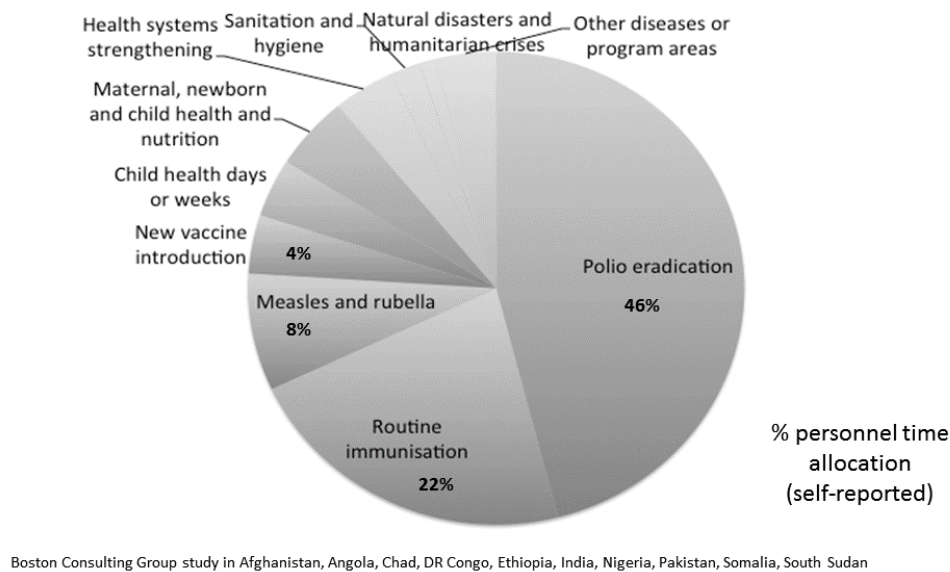


Figure 9. Allocation of polio staff time

Sixteen priority countries (Figure 10) have been identified for polio transition planning with the goal that 14 of these countries develop polio transition plans by end-2016. The plans should provide a roadmap for the transition which should occur during 2017 – 2019 of essential polio functions, resources and lessons learned. These polio transition plans should also include budget commitments from governments and donors to enable the implementation of the plans beginning in 2017.



Figure 10. Sixteen priority countries for polio transition planning

Cochi SL, Hegg L, Kaur A, Pandak C, Jafari H. The global polio eradication initiative: progress, lessons learned, and polio legacy transition planning, *Health Affairs*, 2016;35:277-83.

Measles Rubella Midterm Review Report

Discussion

The 16 priority countries selected for polio transition planning contain most of the world's unvaccinated and under-vaccinated children, as well as most of the world's measles cases and deaths and most of the world's rubella and CRS cases. Immunization system strengthening and measles and rubella elimination are obvious candidates for the transitioning of polio assets. Currently, the polio infrastructure is concentrated in countries with the lowest-performing immunization systems which would benefit from pivoting polio eradication assets to strengthening routine immunization. Many of the strategies used to reach polio eradication are broadly applicable across immunization systems, for example the importance of surveillance laboratory networks, the use of communications and social mobilization, the importance of micro-planning, and the importance of management and accountability. Strategies for measles and rubella control and eradication have other similarities to those for polio eradication, including the importance of outbreak preparedness and response and the need for periodic SIAs to reach inaccessible children. Despite advances, measles and rubella remain high burden diseases: measles is an important cause of deaths in children aged less than five years, and rubella remains the leading infectious cause of birth defects. The ITFDE explicitly recommended that 'countries should adapt infrastructure and resources developed for polio eradication to measles and rubella eradication'.¹¹

At country level, it is important to conduct an inventory of current polio functions and ensure that governments and partners are aware of the possibility of the loss of these functions if they are not transitioned in a timely fashion. The comprehensive multiyear plan (cMYP) should be used as a vehicle for in-country legacy planning and should ensure that there is no weakening of overall immunization programs as a result of the transition. There is a short window of time as polio assets are already beginning to decrease (Figure 11). Although the details of this graph are difficult to see, it clearly demonstrates the marked fall off in overall polio assets anticipated to occur over the next decade.

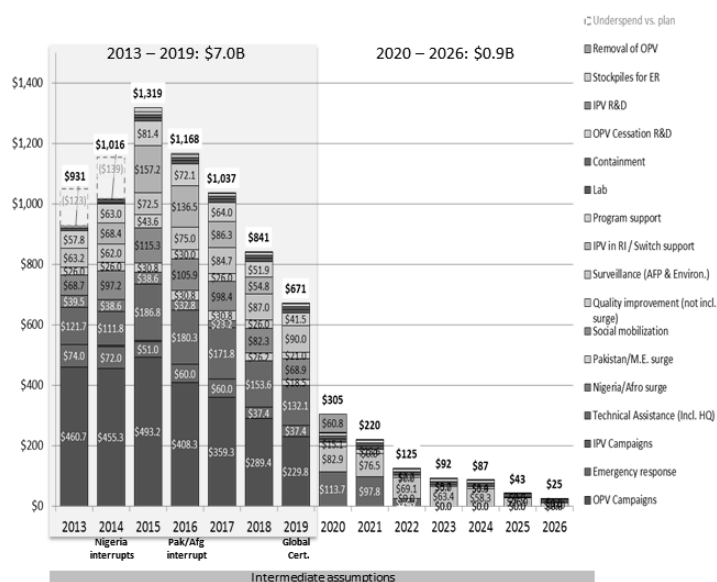


Figure 11. Estimated Costs for Polio Eradication by Activity (USD, not including India self-funded costs). 2013 – 2023

Source: Unpublished data, Financial Resource Requirements, Financial Management Team, Global Polio Eradication Initiative, 2016.

Recommendations

- Given the imminent reduction in polio eradication resources, which can have an adverse impact on both measles and rubella control/elimination efforts, a focus on transition of polio resources is urgent and needs to be a top priority.
- All stakeholders involved in control and elimination of measles and rubella (national governments, M&RI, Gavi, etc.) as well as those involved in immunization system strengthening (BMGF, JSI, CDC, WHO, UNICEF, the World Bank, etc.) should engage in polio transition planning (at all levels) to leverage the opportunity and avoid the risks of the end of the GPEI.
- Strengthening immunization systems and the control and elimination of measles and rubella should be designated as high priorities for polio transition planning and implementation.
- Polio assets should be re-purposed in such a way as to sustain essential polio functions (surveillance, lab network, communications, social mobilization, etc.) as well as the measles, rubella and other immunization functions that they have been supporting. At minimum, there should be no weakening of non-polio activities currently supported by polio assets.
- As part of the country planning framework for immunization and in support of the GVAP goals, a concrete plan with an earmarked budget should be developed and implemented for transitioning essential polio assets to immunization system strengthening and measles and rubella elimination. Under the leadership of the ministries of health, this plan should aim to include the participation of other ministry and all partners with an interest in health system strengthening.

Governance

Background:

National governments have the primary responsibility for management and governance of their national immunization programs. Interagency Coordinating Committees also play a central role in ensuring strong governance of immunization programs in low and lower-middle income countries that rely on external partner support. At regional and national levels, important roles are played by National Verification Committees (NVCs) and RVCs. NVCs scrutinize and monitor progress toward measles and rubella elimination. Annual reports from NVCs are reviewed and feedback provided by independent RVCs. As yet, no global verification committee has been established.

Internationally, two major groups have played critical roles in measles and rubella control and elimination efforts since 2000: the M&RI, originally called the Measles Initiative, and Gavi. The M&RI, formed in 2001 and made up of the UN Foundation, WHO, UNICEF, CDC and ARC, originally aimed to accelerate reduction in measles deaths by expanding the PAHO mass campaign strategies to other regions starting in Africa, where the burden was highest. The M&RI's mission is to globally lead and coordinate efforts to achieve a world without measles and rubella.

Gavi was also formed in 2001 with four founding partners: the Bill & Melinda Gates Foundation, the World Bank, UNICEF and WHO. In contrast to the M&RI, which focuses on measles and rubella, Gavi's mission is to save children's lives and protect people's health by increasing equitable use of vaccines in lower-income countries. Although Gavi's initial focus was introduction of new vaccines, it supported

Measles Rubella Midterm Review Report

measles control activities from 2004-2008 with US\$176 million channeled through the M&RI together with support for introduction of routine measles second dose.

Progress and challenges:

Since its inception, the M&RI has provided more than US\$1.1 billion for measles and rubella control and elimination activities contributing to reduction of measles deaths by 79% by 2014 compared with 2000. In 2013, after a hiatus of five years, Gavi re-engaged in measles and rubella control with support for introduction of rubella vaccine. Gavi's commitment to measles and rubella control was further strengthened when, in December 2015, the Gavi Board approved a new comprehensive measles and rubella strategy with approximately USD 800 million available to Gavi-eligible countries over the period 2016-2020.

Despite the investments made to date in reaching measles and rubella elimination, the 2014 Annual Report on the GVAP concluded that progress towards regional measles and rubella elimination goals was off track and that *"A huge amount of work and political commitment lies ahead if their elimination goals are to be achieved"*³⁸. To build country commitment, the SAGE recommended that each country establish an NVC. RVCs have been actively working in three WHO Regions (Americas, European and Western Pacific) and the SE Asian Region held its first RVC meeting in August 2016. The Table below shows data as of December 2015 summarizing progress towards measles and rubella elimination goals as determined by these RVCs.

WHO Region	Regional Verification Commissions Established	Elimination Achieved	
		No. of Countries	% of Countries
Americas	Yes	Measles: 34 Rubella: 35	97 100
Europe	Yes	Measles: 21 Rubella: 20	40 38
Western Pacific	Yes	Measles: 6	22
Eastern Mediterranean	No	-	-
South East-Asia	No	-	-
Africa	No	-	-

Table 4. Regional Verification Commissions and number of countries verified to have eliminated measles or rubella by WHO Region as of December 2015.

³⁸ World Health Organization. *Global vaccine action plan 2011-2020*. Geneva, World Health Organization (www.who.int/immunization/global_vaccine_action_plan/en, Accessed July 11 2016....).

Discussion

In view of the complementary but sometimes overlapping roles of partners in the M&RI and Gavi, effective mechanisms for coordinating the support provided by global partners to countries are clearly needed to avoid duplication and maximize efficiency. Country ownership is a critical success factor for measles and rubella elimination; examples of such ownership have been shown by the multiple countries within AMR that have largely self-funded measles SIAs in a proactive move to prevent measles outbreaks. Governments have primary responsibility for achieving their measles and rubella goals and must demonstrate this responsibility by providing domestic resources. NVCs and RVCs play an important role in promoting country ownership and accountability. Identifying resources to fill national resource gaps for realistic objectives is a shared responsibility between countries and other stakeholders, including the M&RI and Gavi.

The M&RI has championed measles and rubella vaccination activities globally, advocated for eventual eradication, and while it received funding in the past from donors primarily for mass campaigns and surveillance, funding has dropped dramatically as most donors prefer to give their support for all immunization-related activities to Gavi which is a single agency which can distribute funds to support a range of antigens. Gavi, in turn, has become increasingly supportive of measles and rubella control and the new Gavi measles and rubella strategy offers comprehensive, multi-year support to low income countries that aims to build financial sustainability through increasing country co-financing. However, Gavi's focus is on reduction in morbidity and mortality from measles and rubella and not elimination. This has resulted in differences between Gavi and the M&RI regarding the size and scope of mass vaccination activities (e.g., target age groups for SIAs). In the past, although M&RI may have channeled most of its funding to low-income countries, if needed these funds could, in principle, be available for other countries. The redistribution of funding between the M&RI and Gavi has resulted in this option no longer being available, as Gavi is limited in the countries that it is able to fund.

Recommendations

- It is imperative that there be close collaboration and coordination between Gavi and the M&RI, as a central element in building the overall immunization system and in order to ensure that measles and rubella control and elimination efforts are coordinated and efficient.
- Efforts to control and eliminate measles and rubella should be integrated with the general immunization system and should be used to build and enhance the overall immunization system.
- All countries should establish NVCs to review national progress toward elimination goals, and make recommendations as to how these goals may be met.
- RVCs should be established in all regions where they do not exist and their efforts strengthened in regions in which they do exist. The RVCs should serve as independent reviewers of progress toward measles and rubella elimination and make region and country-specific recommendations to overcome impediments to measles and rubella elimination.

Resource Mobilization

Background

In addition to the resources provided by national governments, funding for measles and rubella control at global level currently has two streams: funding to the M&RI and funding to Gavi. The history of this funding is illustrated in Figure 12.

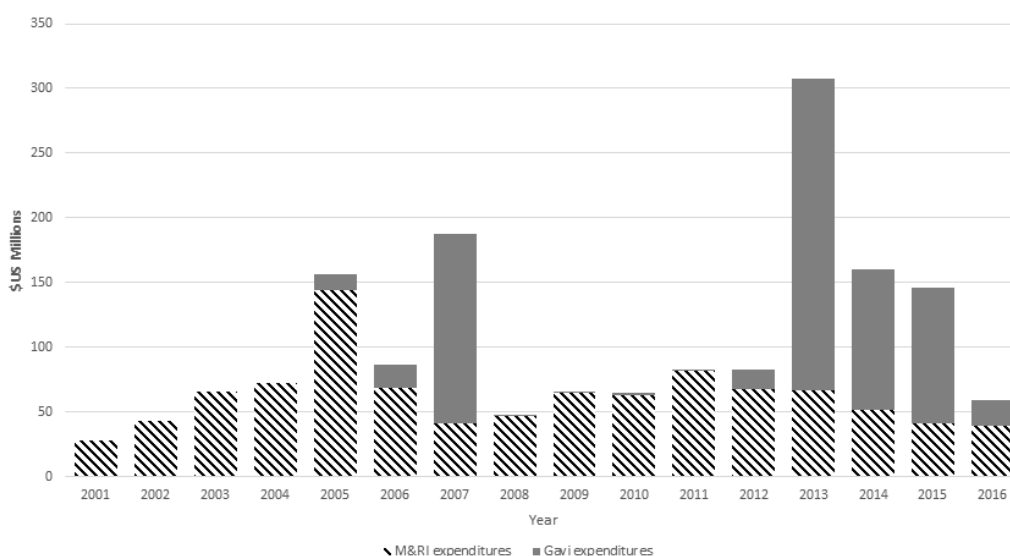


Figure 12. Annual Measles & Rubella Initiative (M&RI) and Gavi Expenditures for Measles and Rubella Control and Elimination Activities, 2001- mid 2016. ³⁹

Funding to the M&RI began in 2001 and increased annually until 2004. A sharp increase occurred in 2005 due to funds brought in by ARC following the Southeast Asian tsunami. In 2004-8, Gavi contributed > USD 175 million through the International Finance Facility for Immunization. However, in recent years the M&RI has seen a steady decline in funding as donors increasingly seek to consolidate all funding given for immunization by giving to a single agency rather than to multiple disease-specific initiatives. The United Kingdom's Department for International Development in its Multilateral Aid Review also cited Gavi's effectiveness in increasing access to immunization, its focus on results, as well as its financial management, accountability checks, and promotion of country ownership.⁴⁰ In contrast to funding through the M&RI, funding from Gavi has recently increased substantially. The spike in Gavi funding in 2013 and the subsequent Gavi funding through 2015 reflects Gavi's commitment to rubella introduction as well as funding for measles-specific activities in six large countries not yet ready to

³⁹ Graph compiled from publicly available web sites.

⁴⁰ Department for International Development. Multilateral Aid Review. March 2011.

www.gov.uk/government/uploads/system/uploads/attachment_data/file/67583/multilateral_aid_review.pdf

introduce rubella. The graph shown above reflects expenditures through mid-2016, and, as a result, most of the funding pledged by Gavi in December 2015 is not reflected.

Progress and challenges

In addition to the funding currently received from national governments, the M&RI partners and Gavi, estimates by the M&RI in October 2015 showed a projected budget shortfall of USD 431 million for the six-year period 2015 – 2020, for an annual average of USD 71 million. This figure includes SIAs and ORI for non-Gavi countries, and surveillance, research and other core functions for both Gavi and non-Gavi countries, but is based on maintaining high level measles control rather than achieving elimination. Since October 2015 when these figures were developed, Gavi has pledged an additional USD 220 million towards these activities.

Discussion

Funding for measles and rubella activities through Gavi for Gavi-eligible countries has increased markedly. However, as noted above, the focus of this funding remains mortality reduction. There remains a need for funding to vaccinate age groups outside of those targeted through Gavi funding. In addition, financing for non-Gavi eligible countries is declining rapidly. Although many countries are able to fund their own measles and rubella control activities, others that have recently graduated from Gavi may be unable to afford the costs of large scale ORI or SIAs. Given the extremely infectious nature of measles, it is very easily transmitted across borders, rendering a global approach to disease control particularly important. If the recommendations from this report are implemented, further funding for strengthening surveillance, research, communications and resource mobilization will be required. In order to advocate for these funds, better estimates of what it would cost to implement these recommendations are required. Initial work on costing the needs for surveillance has begun.

Funds are more likely to be mobilized for measles and rubella elimination if the measles and rubella community can demonstrate how a measles and rubella focus can strengthen health systems overall, and immunization systems in particular. It is also important to remain open to instances in which measles and rubella elimination activities may have been detrimental to health systems overall, and use these situations as opportunities to learn how to avoid such negative interactions in the future.

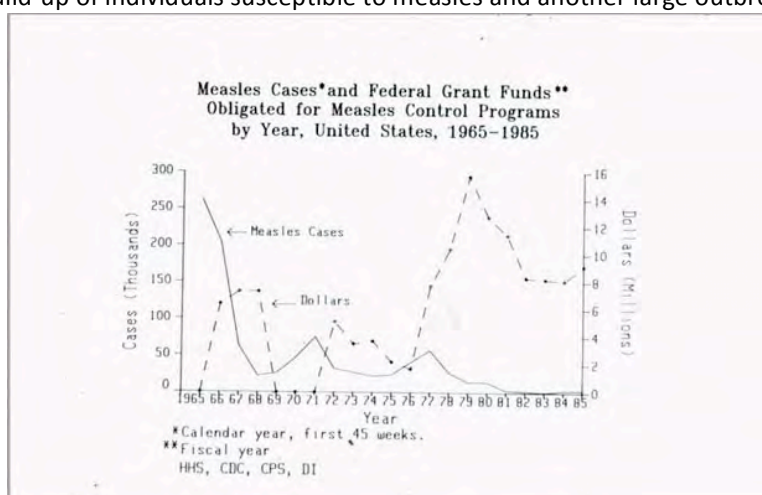
Stable and predictable funding is important to running effective and efficient immunization programs. Frequently, funding for measles and rubella control is most available immediately during and after large outbreaks. However, this funding could usually have been better spent in advance of the outbreak for preventive vaccination. Preventing the outbreak not only prevents the morbidity and mortality as well as the disruption associated with outbreaks, but vaccination activities in non-outbreak settings have more opportunity than those conducted in outbreak settings to be carefully planned, usually resulting in higher coverage and a better return on investment.

In order to mobilize funds, it may be necessary to look beyond the traditional donors to an expanded donor base. This requires investing in adequate staffing for resource mobilization.

□

Lack of stable funding leads to recurrence of disease

In the United States of America, a recurrent funding and disease cycle occurred before funding was stabilized and dependably available for adequate preventive vaccination. In this cycle, measles outbreaks led to increased funding for measles control which then resulted in decreased measles cases and a perception by policy makers that funding could be decreased. This decrease in funding in turn led to a build-up of individuals susceptible to measles and another large outbreak.



Source: Orenstein WA. The role of measles elimination in development of a national immunization program. *Pediatric Infectious Disease Journal* 2006 Dec;25(12):1093-101

Recommendations

- A multi-year Financial Resource Requirements (FRR) document for measles and rubella in the context of the overall immunization system should be developed. The FRR should include demand-driven, country driven projections on need, and reflect funding from Gavi, the M&RI, other partners and domestic financing. This document should be complemented by yearly work plans with detailed national partners' financial contributions.
- The recent welcome additional support from Gavi for measles and rubella activities provides a major step forward for achieving measles and rubella goals. However, it is not, in itself, sufficient to provide adequate assistance globally, as many countries are not Gavi-eligible or are graduating from Gavi-eligibility and key global strategies such as surveillance and research are under-resourced. Consequently, there is a need for additional funding.
- The five M&RI founding partners should have adequate staff capacity to identify and align the resources needed and mobilize additional donors and resources to fill the funding gap for immunizations overall and measles and rubella vaccination in particular.
- Country co-financing for measles and rubella activities should increase as countries move along the development continuum. Country financial commitments should be closely followed through the annual work plan budget.
- Efforts should be made to identify examples of when a focus on measles and rubella elimination has led to building of the overall immunization system (e.g., where a focus on measles and

rubella led to a school entry check for those vaccines as well as other vaccines recommended for children, leading to improved coverage for all recommended vaccines). In addition, it is important to remain open to examples of when a focus on measles and rubella has had a negative impact on overall healthcare and immunization systems, and learn from any such examples how such a situation can be avoided.

SECTION 6. SUMMARY

In summary, tremendous progress has been made towards both measles and rubella elimination since 2001. Significant gains have also been made during the period 2012 – 2015. However, despite these advances, neither measles nor rubella elimination are on track to achieve the ambitious goals laid out in the *Global Measles and Rubella Strategic Plan, 2012-2020*. The basic strategies articulated in this document are sound, but full implementation of them has been limited by lack of country and global political will and country ownership, reflected in insufficient resources. In principle, the 2020 goals can still be reached, but doing so would require a substantial escalation of political will and resources as well as heavy reliance on SIAs. Elimination, once achieved, would be difficult to sustain without more robust routine immunization systems than currently exist in much of the world. This report recommends focusing on improving ongoing immunization systems --although this may delay reaching measles and rubella elimination goals -- in order to ensure that gains in measles and rubella control can be sustained. Re-orienting the measles and rubella elimination program to increase emphasis on surveillance so that programmatic and strategic decisions can be guided by data is critical.

The inextricable linkage between achieving and maintaining measles and rubella elimination and strong immunization systems is also repeatedly underlined in this report. Measles incidence is recognized as a marker of the health of immunization systems, and of health systems overall. Because of its ability to detect unreached populations and program weaknesses, measles also serves as an indicator disease, or the ‘canary in the coal mine’, a characteristic whose importance has recently been highlighted in the context of global health security.⁴¹ A focus on measles and rubella elimination can result in gains across the immunization system, as is well described by Orenstein^{42,43} and as occurred in China where school entry –checks to ensure measles vaccination were expanded to check all recommended vaccines.⁴⁴

⁴¹ Berkley S. Measles – the canary in the coal mine. 27 April 2016. Devex. (<https://www.devex.com/news/measles-the-canary-in-the-coal-mine-88044>, Accessed July 9 2016).

⁴² Orenstein WA. The role of measles elimination in development of a national immunization program, *Pediatric Infectious Disease Journals*, 2006, 25(12):1093 –1101.

⁴³ Orenstein WA, Seib K. Beyond Vertical and Horizontal Programs: a Diagonal Approach to Building National Immunization Programs through Measles Elimination. *Expert Review of Vaccines*, 2016, 15(7):791-793 (<http://www.tandfonline.com/doi/full/10.1586/14760584.2016.1165614>. Accessed 8 August 2016).

⁴⁴ Zuo S, Cairns L, Hutin Y, Liang X, Zhu Q, Lee LA, et al. Accelerating measles elimination and strengthening routine immunization services in Guizhou Province, China, 2003-2009. *Vaccine*, 2015, Apr 21; 33(17):2050-2055.

**Conclusions of the SAGE Working Group on Measles and Rubella
August 25-26, Geneva**

**WHO Policy Recommendation on Routine Measles Second Dose (MCV2):
Considerations for Removing the Criterion for Introduction**

□

FOR DECISION

In light of the following considerations and in the interest of advancing progress towards measles control and elimination, SAGE is requested to consider whether it is appropriate at this time to remove the introduction criterion for MCV2 published in the 2009 WHO Measles Vaccine position paper¹.

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Definitions

“First dose” and “second dose” refer to the doses of measles-containing vaccine an individual receives and, thus, have implications for the likelihood that a vaccinated individual is protected against measles.

“MCV” refers to measles-containing vaccine, which can include measles, measles-rubella, measles-mumps-rubella, or measles-mumps-rubella-varicella vaccines.

“MCV1” and “MCV2” refer to “measles-containing vaccine dose 1” and “measles-containing vaccine dose 2”. These are programmatically scheduled vaccinations, which can be delivered through routine services, intensification of routine services, or supplementary immunization activities (SIAs).

In this document use of the term “MCV1” implies delivery through routine services. Because MCV2 can be delivered in routine or campaign mode, the term “routine MCV2” will be used to refer to the 2nd dose of measles-containing vaccine delivered through routine services. MCV1 and MCV2 refer to any of measles-containing vaccine formulations.

Background

WHO’s current policy recommendation, as provided in the 2009 Measles Vaccine Position Paper¹, is that all children should receive two doses of measles-containing vaccine:

“Reaching all children with 2 doses of measles vaccine should be the standard for all national immunization programmes.”

The position paper provides the following criterion for introduction of routine MCV2:

“MCV2 may be added to the routine immunization schedule in countries that have achieved >80% coverage of MCV1 at the national level for 3 consecutive years as determined by the most accurate means available. In general, countries that do not meet this criterion should prioritize improving MCV1 coverage and conducting high-quality follow-up supplemental immunization activities (SIAs), rather than adding MCV2 to their routine schedule.”

This policy guidance gives clear direction to countries with low coverage of MCV1 to focus their efforts on improving first dose coverage before introducing a second in the national schedule. The rationale underpinning this recommendation was the high effectiveness of one dose of MCV delivered at 9 months of age or older, and the expectation that children in countries without routine MCV2 would receive a second dose of measles-containing vaccine through supplementary immunization activities. Findings from the 3rd Meeting of the SAGE Working Group on Measles (2009) indicate that although countries with lower starting MCV1 levels were able to increase their routine MCV2 coverage during the first 5 years after introduction, their performance remained highly variable and their median routine MCV2 value never reached > 90%. Thus,

¹ WHO 2009. *Measles Vaccines: WHO Position Paper*. WER No. 35, 2009. 84. Pp. 349-360.

working group members felt that countries with weaker systems would not be able to achieve high coverage with a second measles dose delivered through routine services². This policy guidance gives clear direction to countries with low coverage of MCV1 to focus their efforts on improving first dose coverage before introducing a second in the national schedule.

With respect to stopping SIAs, the WHO recommendation in the 2009 Measles Position Paper specifies:

“The cessation of SIAs should be considered only when >90-95% immunization coverage has been achieved at the national level for both MCV1 and routine MCV2 for a period of at least 3 consecutive years”.

Thus, in countries not meeting the MCV2 introduction criterion, SIAs should continue to be the means of providing a second dose of MCV, while in countries with MCV2 in the routine schedule, SIAs will still be needed until national coverage levels with the two routine doses reaches levels higher than 90%.

The position paper also provides guidance regarding the optimal timing of routine delivery of MCV2:

“Countries with ongoing measles transmission and MCV1 delivered at age 9 months should administer the routine dose of MCV2 at age 15–18 months. The minimum interval between MCV1 and MCV2 is 1 month. Providing routine MCV2 to children in their second year of life reduces the rate of accumulation of susceptible children and the risk of an outbreak. In countries with low measles transmission (that is, those that are near elimination) and where MCV1 is administered at age 12 months, the optimal age for delivering routine MCV2 is based on programmatic considerations that achieve the highest coverage of MCV2 and, hence, the highest population immunity. Administration of MCV2 at age 15–18 months ensures early protection of the individual, slows accumulation of susceptible young children and may correspond with other routine immunizations (for example, a DTP booster). If MCV1 coverage is high (>90%) and school enrolment is high (>95%), administration of routine MCV2 at school entry may prove an effective strategy for achieving high coverage and preventing outbreaks in schools.”

Finally, the position paper outlines a policy on catch-up vaccination at school entry:

“Irrespective of the strategy or schedule followed, both MCV1 and MCV2 should be recorded on a child’s immunization card and in a clinic’s vaccination register. Children should be screened for their measles vaccination history at the time of school entry, and those lacking evidence of receipt of 2 doses should be vaccinated.”

The rubella position paper recommends that when rubella vaccine is introduced and combined with measles vaccine, the same formulation of combined MR or MMR vaccine should be used for both doses:

“However, when combined with measles vaccination, it may be easier to implement a second dose of rubella-containing vaccine (RCV) using the same combined MR vaccine or MMR vaccine for both doses.”³

With the accumulation of 6 years of implementation experience, there are a number of considerations that have emerged which call into question the continued usefulness of the MCV2 introduction criterion. During its August 2016 Meeting, the SAGE Working Group on Measles and Rubella (SAGE MR WG) reviewed the evidence and experience related to the criterion for the introduction of MCV2 into routine immunization schedules.

Based on this review, the SAGE MR WG recommends that the criterion for introduction of routine MCV2 be removed. Other recommendations related to routine MCV2, such as the optimal timing, recording doses, school entry, use of rubella-containing vaccines with routine MCV2, were not reviewed and remain unchanged.

² WHO 2009. *Report from the 3rd Meeting of the SAGE Working Group on Measles*, 2009.

³ WHO 2011. *Rubella Vaccines: WHO Position Paper*. WER No. 29, 2011, 86, Pp. 301–316.

Current Status of Measles Coverage Related to Routine Measles Second Dose Introduction:

Routine MCV2 introduction

As of December 2015, the vast majority of countries in the world are implementing a 2-dose routine measles vaccination schedule (160/194, or 82% of countries) and global coverage of MCV2 is estimated at 61%. Of the 33⁴ countries yet to introduce MCV2 into their national immunization schedule, 10 already meet the WHO MCV2 introduction criteria (Bolivia, Comoros, Congo, Dominican Republic, Honduras, Lao People's Democratic Republic, Namibia, Nicaragua, Solomon Islands and Uganda). For the remaining 23 countries, 6 have high or improving coverage, and are close to meeting the introduction criterion; 7 have MCV1 coverage close to 70% or above; and 10 have low coverage (Table 1). Of these 23 countries, 18 are in the WHO Africa Region.

Table 1. Countries that have not introduced routine MCV2 and do not meet routine MCV2 introduction criterion, MCV1 coverage (WUENIC estimates)

Country	WHO Region	MCV1 2013	MCV1 2014	MCV1 2015
MCV1 coverage close to introduction criterion				
Guatemala	AMRO	85	67	99
Togo	AFRO	72	82	85
Cameroon	AFRO	83	80	79
Democratic Republic of the Congo	AFRO	76	77	79
Ethiopia	AFRO	62	70	78
Mali	AFRO	80	80	76
Lower MCV1 coverage				
Benin	AFRO	68	68	75
Côte d'Ivoire	AFRO	76	62	72
Mauritania	AFRO	80	84	70
Timor-Leste	SEARO	70	74	70
Gabon	AFRO	70	61	70
Guinea-Bissau	AFRO	69	69	69
Liberia	AFRO	74	58	64
Lowest MCV1 coverage				
Chad	AFRO	59	54	62
Madagascar	AFRO	63	64	58
Nigeria	AFRO	47	51	54
Haiti	AMRO	65	53	53
Vanuatu	WPRO	53	53	53
Guinea	AFRO	62	52	52
Central African Republic	AFRO	25	49	49
Somalia	EMRO	46	46	46
Equatorial Guinea	AFRO	42	44	27
South Sudan	AFRO	30	22	20

Routine MCV2 coverage after introduction of the second dose

The accumulated evidence demonstrates that both groups of countries (those meeting and those not meeting the introduction criterion) show a trend of increased routine MCV2 coverage during the first five years after introduction. Unsurprisingly, countries with stronger systems that had higher MCV1 coverage at the time of routine MCV2 introduction also achieve higher levels of routine MCV2 coverage (Figure 1). Similar trends are also observed when restricting the analysis to countries that have the routine MCV2 in the second year of life and are thus providing the second dose through routine vaccination services rather than other means which may be more likely with school entry vaccination (Figure 2).

⁴ Note that Papua New Guinea introduced routine MCV2 in January 2016, and was excluded

Figure 1. MCV2 coverage during the first five years after MCV2 introduction (1999-2014), all countries (WUENIC estimates)*

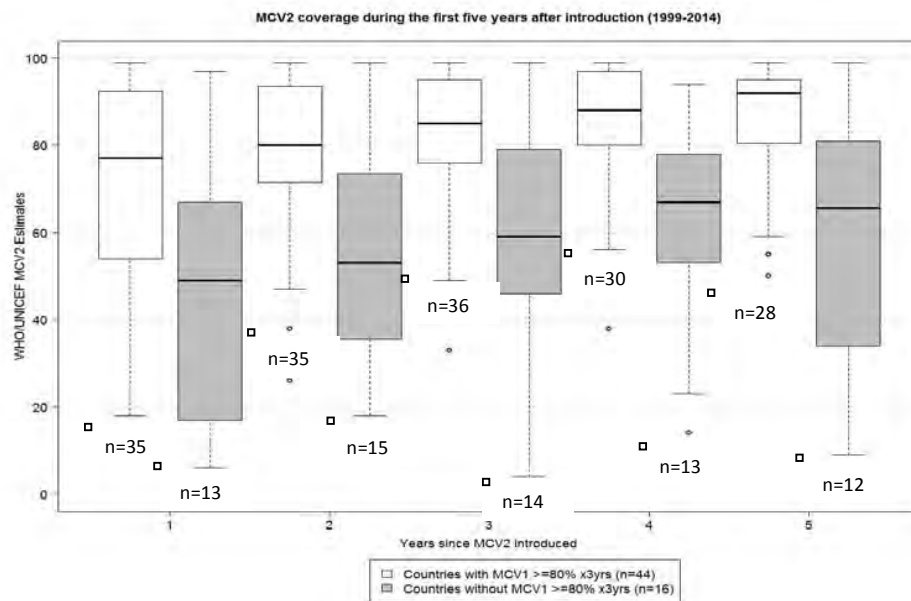
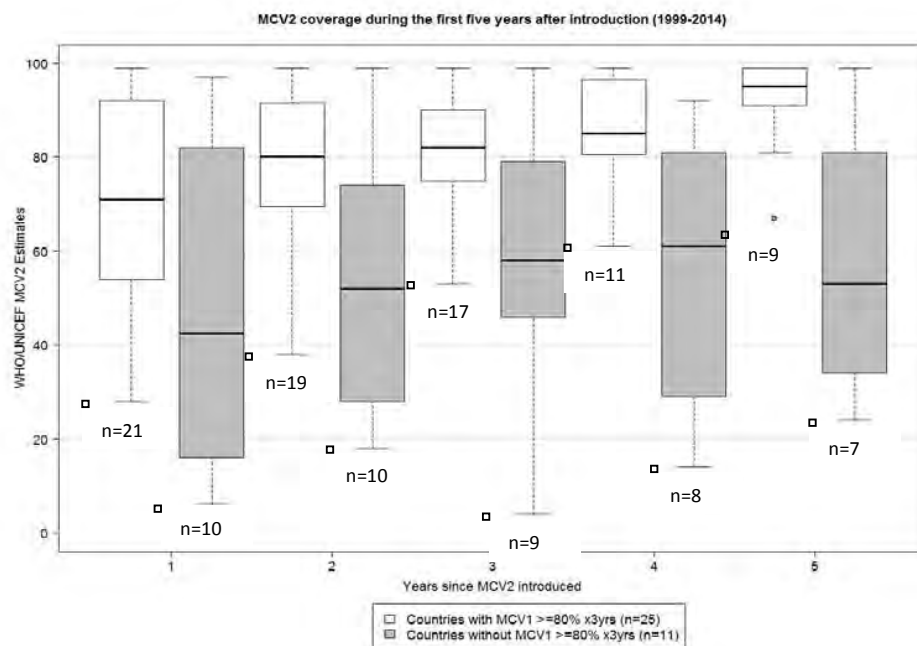


Figure 2. MCV2 coverage during the first five years after MCV2 introduction (1999-2014), countries with routine MCV2 in second year of life (WUENIC estimates)*



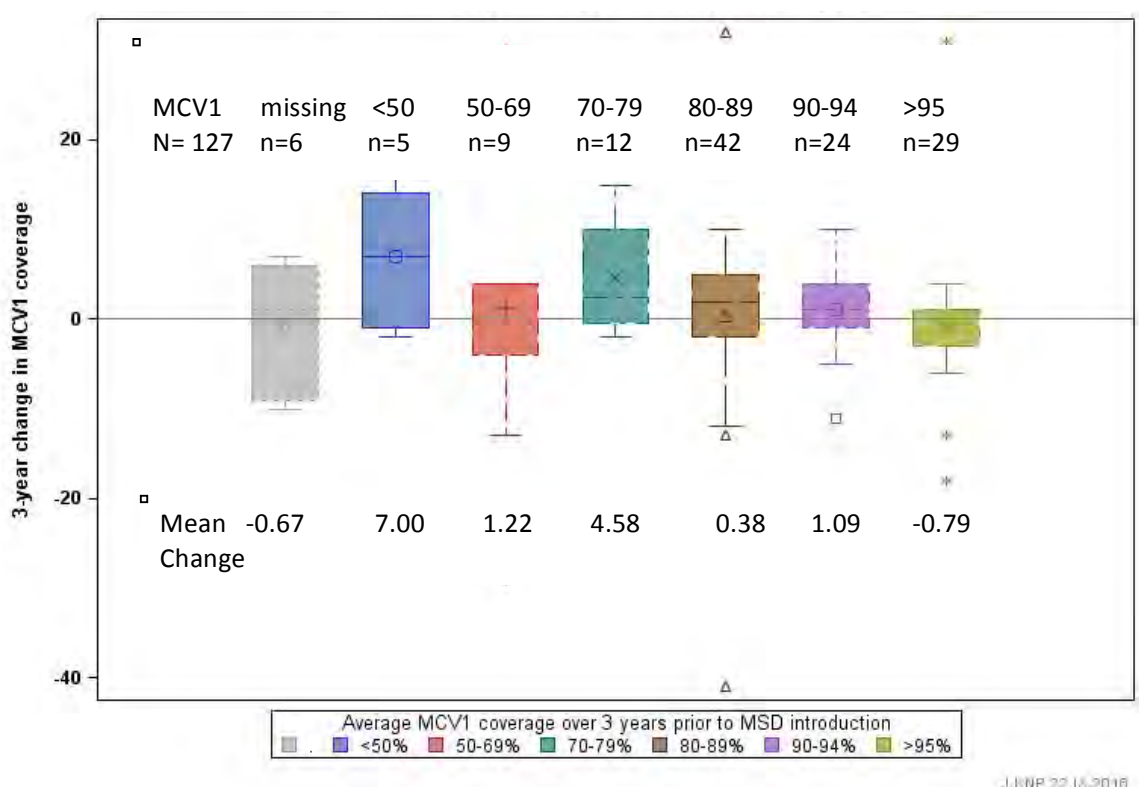
* Figures 1 and 2 display median MCV2 coverage for the 5 years after MCV2 introduction, along with 25-75% interquartile ranges. Figure 1 displays all countries and Figure 2 is restricted to those countries with MCV2 in the routine schedule between 12 and 23 months of age. The range of introduction years, 1999-2014, were selected based on the availability of WUENIC routine MCV2 estimates. If countries introduced routine MCV2 over several years, the nationwide year of introduction was considered the introduction year. Not all countries contributed 5 years of trend data. Those that introduced MCV2 after 2010 have not accumulated 5 years of MCV2 WUENIC estimates. In addition, for some countries, MCV2 estimates were not generated for the years immediately following introduction, due to the absence of reporting data. In both figures, MCV2 estimates are included for the years available; the total number of countries contributing data in each category is indicated in text boxes. The countries in both figures are separated according to whether they had achieved at least 80% MCV1 coverage for three consecutive years prior to introduction (white boxes) compared with countries which did not achieve this MCV1 coverage level (gray boxes). *Acknowledgments: Sebastian Antoni, Laure Dumolard*

MCV1 coverage after routine MCV2 introduction

Despite concerns that MCV2 may divert resources from improving MCV1 coverage, pooled data provide no evidence of this. As shown in Figure 3, countries with an MCV1 level <80% at the time of MCV2 introduction show a more marked improvement in median MCV1 coverage for the three years following MCV2 introduction relative to the three years preceding, compared to countries with MCV \geq 80%. While no causal relationship is implied by these data, at least there is no evidence that MCV2 introduction causes harm to MCV1 coverage.

Five countries introduced routine MCV2 with a median MCV1 coverage <50% for the three years preceding introduction. The changes in median MCV1 for these countries are as follows: Iran 1984, +17%; United Arab Emirates 1985, +14%; Mongolia 1989, -2%; Papua New Guinea 1999, -1%; and Afghanistan 2004, +7%.

Figure 3. Mean change in median MCV1 coverage, three years preceding and three years following routine MCV2 introduction, by MCV1 level at the year of introduction, through 2012 (JRF estimates)*



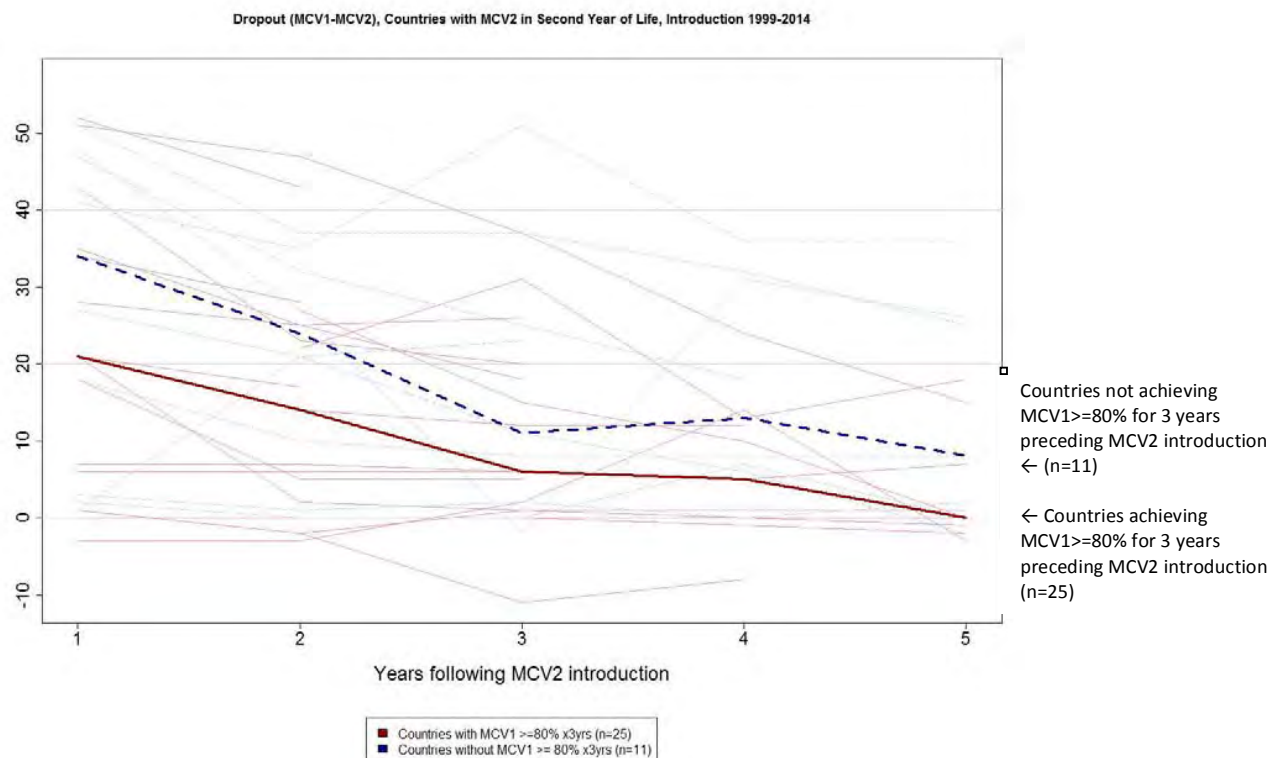
* Figure 3 displays the mean change by country groupings in the median MCV1 level for the three years preceding compared with the three years following MCV2 introduction, with 25-75% interquartile ranges. Countries are grouped by the median level of MCV1 coverage for the three years preceding routine MCV2 introduction, as reported on the Joint Reporting Form. Categories from left to right: MCV1 missing; <50; 50-69; 70-79; 80-89; 90-94; >95. *Acknowledgments: Jennifer Knapp*

MCV1-MCV2 dropout after routine MCV2 introduction

The difference between MCV1 and MCV2 coverage (drop-out) at the country level in the five years after introduction is shown in Figure 4, among countries with routine MCV2 in the second year of life.

Regardless of the MCV1 coverage levels at the time of introduction, the difference between MCV1 and MCV2 declines over the five years after introduction. However, dropout is lower for countries meeting the introduction criterion, compared to countries not meeting the criterion.

Figure 4. MCV1-MCV2 dropout (difference between MCV1 and MCV2 coverage) during the 5 years following routine MCV2 introduction, 1999-2014, countries with MCV2 in the second year of life (WUENIC estimates)*



* Figure 4 displays MCV1-MCV2 dropout rates (the difference between national MCV1 and MCV2 coverage, WUENIC estimates) during the 5 years after routine MCV2 introduction, restricted to those countries with MCV2 in the routine schedule between 12 and 23 months of age. The range of introduction years, 1999-2014, were selected based on the availability of WUENIC routine MCV2 estimates. If countries introduced routine MCV2 over several years, the final year of introduction was considered the introduction year. Not all countries contributed 5 years of trend data. Those that introduced MCV2 after 2010 have not accumulated 5 years of MCV1 and MCV2 WUENIC estimates. In addition, for some countries, MCV2 estimates were not generated for the years immediately following introduction, due to the absence of reporting data. Dropout rates are included for the years available. The countries in both figures are separated according to whether they had achieved at least 80% MCV1 coverage for three consecutive years prior to introduction (solid red lines) compared with countries which did not achieve this MCV1 coverage level (dashed blue lines). Median dropout rates by category of meeting or not meeting the introduction criterion are shown in the bold lines with respective styles and colors.

Factors for Considerations:

Overall, countries with weaker immunization systems and which met the 2009 criterion for MCV2 introduction (at least 80% MCV1 coverage for 3 years preceding introduction) had poorer MCV2 performance, as measured by MCV2 coverage and MCV1-MCV2 dropout. This observation holds true for countries introducing MCV2 prior and subsequent to the publication of the 2009 recommendation.

Notwithstanding the relative overall poorer performance of countries not meeting the introduction criterion, a number of considerations compel the SAGE MR WG to recommend removing the introduction criterion, both to help increase population immunity to measles and for programmatic purposes. Below is a summary of the factors considered.

Equity in access to vaccines

In countries that do not meet the MCV2 introduction criteria, children born between campaigns do not have equitable access to two doses of measles vaccine. The current recommendation is that reaching all children with 2 doses of measles vaccine should be the standard for all national immunization programmes. However,

depending on the timing of their birth, some children have to wait up to three years for the next follow up campaign in order to receive a second dose of measles vaccine.

Particularly in settings in which measles virus continues to circulate (which describes most countries without routine MCV2), children who either do not receive a first dose or who fail to seroconvert are at risk of contracting measles. The absence of routine MCV2 likely increases the interval before they receive a dose through supplementary services and thus decreases their access to measles vaccine and increases their risk of morbidity and mortality associated with measles. Parents/guardians have the right to access a primary vaccination schedule that provides full individual protection for their children, regardless of when they are born.

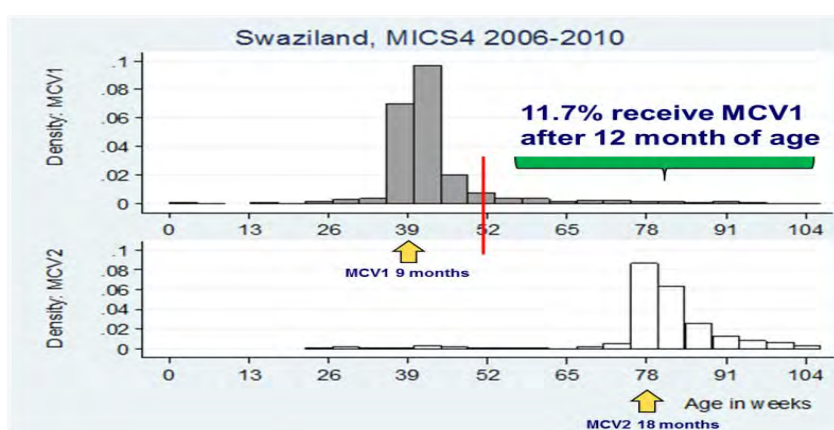
Overcoming barriers to vaccination beyond 12 months of age

Adding a routine measles dose during the second year of life may in fact increase MCV1 coverage as more children access vaccination services and barriers to administering a dose of measles vaccine after 12 months of age are overcome. Ad hoc reports indicate that many developing countries limit vaccination services to infants <12 months of age, and do not offer vaccination to children older than 12 months who come late or are missing doses. This is mainly due to fear of running out of vaccine and lack of knowledge about the need to provide measles vaccination to any non-immune person, irrespective of their age. Having routine MCV2 in the 2nd year of life signals to health workers that measles vaccination is indicated and catching up MCV1 beyond 12 months of age is in fact good practice. The data indicate that routine MCV2 likely does not adversely impact MCV1 coverage (Figure 3); routine MCV2 may in fact increase the number of children who receive MCV1.

Furthermore, when a second dose of MCV is administered to children over one year of age who failed to develop protective antibody levels (primary vaccine failure) following the first dose, the majority (median proportion, 97%; interquartile range, 87-100%)⁵ will develop protective antibody levels. For those who missed receiving their MCV1 dose entirely, a 2-dose schedule allows for them to be caught-up at the 2nd contact and because they will be > 12 months a higher proportion (90-95%) will develop protective antibodies compared to those receiving their first dose at 9 months (85%).⁶

Unfortunately, data on MCV1 doses administered late are not routinely collected through the JRF system, and only recently are being assessed by more systematic surveys such as MICS or DHS. An analysis of MICS data for Swaziland on the timeliness of vaccination for their 2-dose MCV schedule shows that more than 10% of children receive their first dose of MCV1 when they are older than 12 months (Figure 5).

Figure 5. Age of receipt of MCV1 and MCV2, Swaziland, MICS4 2006-2010



⁵ WHO 2009. *Measles Vaccines: WHO Position Paper*. WER No. 35, 84. Pp. 349-360.

⁶ WHO 2009. The immunological basis for immunization series - Module 7: Measles - Update 2009. http://apps.who.int/iris/bitstream/10665/44038/1/9789241597555_eng.pdf

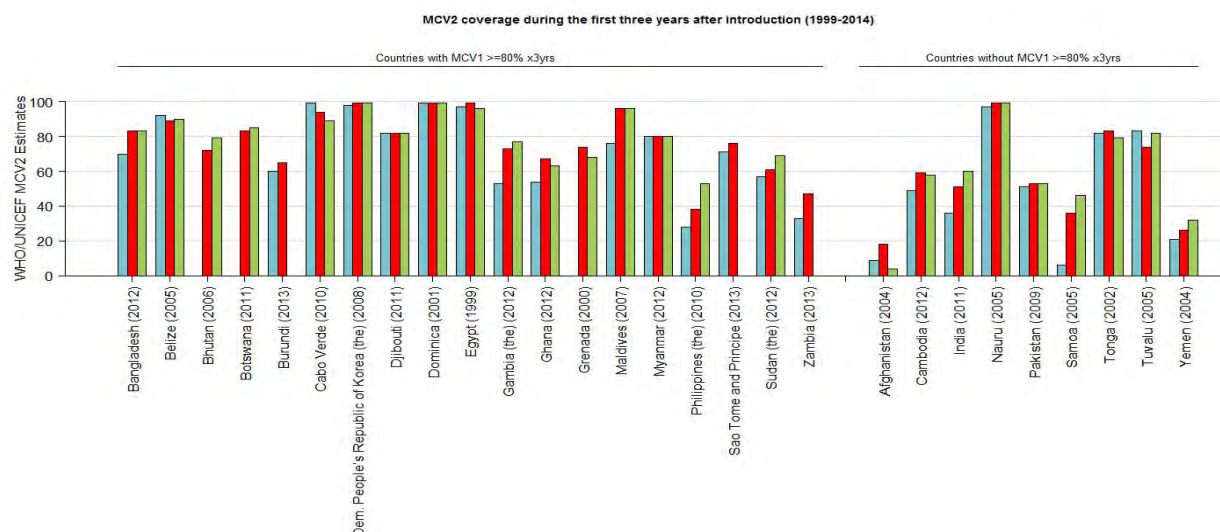
Building a 2nd year of life platform

An MCV2 contact at 15 – 18 months can help build a 2nd year of life platform, which can be used for delivering other vaccines (e.g. Men A; PCV if using a 2+1 alternative schedule, DTP4 booster doses). An MCV2 contact can also be used for catching up any missed vaccination doses and therefore help towards improving completion of the immunization schedule and fully immunized child (FIC) coverage.

Country experiences show time is needed to ramp up MCV2 coverage

Country experiences indicate for many countries, it takes a number of years to ramp up coverage levels for routine MCV2. Generally, routine MCV2 coverage increases gradually over 3-5 years as the programmatic and operational aspects are worked out. Delaying the “learning by doing” and systems strengthening needed to deliver routine MCV2 further extends the length of time that a routine 2 dose schedule is unavailable.

Figure 6. MCV2 coverage for 3 years following MCV2 introduction, 1999-2014, countries with MCV1 ≥ 80% for 3 consecutive years prior to MCV2 introduction and countries not achieving MCV1 ≥ 80% for 3 consecutive years prior to MCV2 introduction (WUENIC estimates)



Creating consistency in primary vaccination schedule recommendations

Although the WHO Position Paper clearly states that two doses of MCV are required, the restrictive MCV2 introduction criterion does not enunciate a clear recommendation with regards to the measles routine schedule, and may imply that a second dose is not truly required. All other WHO vaccination recommendations clearly specify the number of doses required for the primary series (e.g. 3 doses of DTP) irrespective of the delivery strategy. WHO's measles vaccination policy recommendation does not have this precision, which may result in the misunderstanding that the 2nd dose is a booster dose rather than a primary schedule. Many countries are not yet implementing booster doses for any vaccines.

In addition, the provision of delivery strategy options (routine or SIA) in the recommendation sends a mixed message about the 2-dose schedule. By definition, all nonselective SIAs provide “supplemental doses” which are not counted towards the completion of a child's immunization schedule. Despite guidance on recording SIA doses, in reality this is rarely done in many regions. As such, the SIA delivery strategy option is equivalent to a “second opportunity” rather than a “second dose” for all children.

Reducing MCV wastage

Removing impediments to MCV2 introduction may reduce wastage. Most developing countries are using 10-dose vials of measles vaccine. Because of the need to follow the multi-dose vial policy⁷, vaccine wastage rates for developing countries with 1-dose MCV schedule are high, ranging between 45-65%.

It is estimated that the introduction of MCV2 (switching from a 1-dose to a 2-dose schedule) may reduce current measles vaccine wastage rates by almost 40% (to 25-35%) (Figure 7). This reduction in vaccine wastage rates has been confirmed by a detailed analysis of country data from Niger and Senegal. Both countries use yellow fever vaccine (1 dose schedule at 9 months; 10 dose vial) and MCV (2-dose schedule 9 and 18 months; 10 dose vial). Comparing vaccine wastage rates where coverage for MCV1 and YF are equivalent, and where reliable wastage data are available, MCV wastage rate was 40% less in Niger (national) and 62% less in Senegal (2 regions) compared to wastage rates for yellow fever (Annex 1). The reduction in MCV wastage rates for a 2-dose schedule was consistent even when MCV2 coverage was quite low.

For those countries that are still following a 1-dose MCV schedule, unused measles doses could be used to provide a 2nd dose to older children. The resulting reduction in MCV wastage rates may help to overcome the hesitation or fear that some health workers have to open vials for a few children.

Figure 7: Estimated wastage rates for 1 and 2-dose measles schedules, by vial size⁸

Vial size	For 1 dose schedule		For 2 dose schedule	
	Estimated wastage rate	Estimated wastage factor	Estimated wastage rate	Estimated wastage factor
Single dose	<5%	1.05	<5%	1.05
5 doses/vial	30–40%	1.43–1.67	15–25%	1.18–1.33
10 doses/vial	45–60%	1.82–2.50	25–35%	1.33–1.54

Improve recording of doses

Finally, routine MCV2 may improve dose recording. WHO recommends that recording and monitoring the administration of all MCV doses is required, including those delivered through mass campaigns. However, only in the Region of the Americas and Europe are campaign doses of measles vaccine regularly recorded. Non-recording of SIA doses in many measles endemic countries means that there is an incomplete record of the number of doses children have received. For improved measles control and ultimate elimination, it is important to accurately know number of doses received for case investigation and generation of population immunity profiles. Recommending a two-dose routine schedule for all countries (without any introduction criteria) would globally standardize the recording of at least two doses.

Draft Recommendations

The following recommendations are proposed by the SAGE WG on Measles and Rubella for considerations by the SAGE based on the evidence and programmatic factors described above.

- All countries should include two doses of MCV in the routine schedule; MCV2 should be added to the routine immunization schedule in all countries regardless of MCV1 coverage. The optimal timing for the age of administration for routine MCV2 remains unchanged from current recommendations. Routine MCV2 can serve to establish a well-child visit in the second year of life and provide a timely opportunity to catch-up children who missed MCV1.

⁷ Multi-dose vial policy: Once measles vaccine has been reconstituted, the vial must be discarded at the end of each immunization session or at the end of six hours, whichever comes first.

⁸ Detailed guidance for MCV2 introduction is available in “A Guide to Introducing a Second Dose of Measles Vaccine into Routine Immunization Schedules” World Health Organization, 2013. Available at www.who.int/vaccines-documents/

- Before introduction of routine MCV2, countries should determine a suitable age for administration of this dose and establish a system for recording doses both for the individual (e.g., an immunization card) and for the health system (e.g., a vaccination register). Training of health staff should be conducted to ensure timely scheduling of doses and tracking defaulters. Both MCV1 and MCV2 should be recorded on a child's immunization card and in a clinic's vaccination register, and both should include documentation of the age of MCV1 and MCV2 receipt. The first dose of MCV received should be recorded as MCV1, regardless of the child's age at the time of receipt. Any MCV dose administered as supplemental rather than routine should be recorded as a supplemental dose. Children should be screened for their measles vaccination history at the time of school entry, and those lacking evidence of receipt of 2 doses should be vaccinated.
- Because addition of routine MCV2 only covers a single birth cohort and will take time to achieve high coverage, countries should not stop regular follow-up SIAs of measles-containing vaccines. Accumulation of susceptible persons should continue to be monitored subsequent to routine MCV2 introduction and a follow-up SIA conducted whenever the number of susceptible pre-school age children approaches the size of a birth cohort. Furthermore, subnational coverage data should be monitored for the unequal accumulation of susceptible children, indicating equity gaps. Routine MCV2 will slow the accumulation of susceptible children and thereby lengthen the inter-SIA interval, decrease reliance on SIAs and eventually stop SIAs once high coverage (>95%) can be maintained with a routine two dose schedule.

Annex 1: Comparison of yellow fever vaccine (1 dose) and MCV (2 dose) wastage rates

NIGER (summary data for all regions)									
Régions	Districts	Monthly Surviving Infants	# Health Posts	Cumulative coverage, as May 2016			Wastage rates (May-16)		Difference in wastage YF (1dose) compared to MCV (2dose)
				MCV1	MCV2	YF	MCV	YF	
AGADEZ	4 Districts	1,976	65	83%	24%	82%	8.4%	13.4%	37%
DIFFA	3 Districts	3,277	50	92%	25%	92%	9.0%	12.3%	27%
DOSSO	5 Districts	9,791	124	89%	35%	90%	7.2%	32.7%	78%
MARADI	7 Districts	17,498	145	91%	46%	89%	9.3%	18.1%	49%
TAHOUA	8 Districts	14,315	151	95%	34%	95%	10.2%	13.9%	27%
TILLABERI	6 Districts	12,764	184	91%	25%	90%	11.5%	13.8%	17%
ZINDER	6 Districts	20,454	136	89%	33%	87%	8.0%	8.2%	3%
NIAMEY	5 Districts	4,373	44	79%	9%	81%	6.6%	8.3%	20%
National Weighted Average				90%	33%	89%	9.0%	15.2%	40%
SENEGAL (data for two regions)									
Régions	Districts	Monthly Surviving Infants	# Health Posts	Cumulative coverage, as March 2016			Wastage rates (March-16)		Difference in wastage YF (1dose) compared to MCV (2dose)
				MCV1	MCV2	YF	MCV	YF	
Kedougou	Kedougou	252	11	28%	25%	28%	12%	27%	54%
Kedougou	Salemata	71	7	5%	3%	5%	22%	27%	18%
Kedougou	Saraya	163	11	15%	10%	14%	17%	37%	54%
Kolda	Kolda	784	25	67%	59%	68%	16%	36%	55%
Kolda	Medina Yoro Foulah	396	13	49%	49%	49%	4%	25%	85%
Kolda	Velingara	887	20	84%	71%	84%	5%	18%	74%
Regional Weighted Average				61%	54%	61%	10.2%	27.1%	62%

**Report of the SAGE Working Group on
Maternal and Neonatal Tetanus
Elimination and Broader Tetanus
Prevention**

September 2016

Table of contents

List of Abbreviations.....	ii
Executive Summary.....	1
Background.....	2
Tetanus disease.....	2
Tetanus disease burden	2
Sustaining MNTE	9
Broader Tetanus Prevention.....	10
Population immunity following routine immunization and SIAs	11
Evidence shows need for improving coverage for primary doses of TTCV	12
Evidence shows need for providing booster doses of TTCV	13
Improved surveillance for tetanus cases needed.....	13
Proposed revision of the WHO Tetanus position paper.....	16
Conclusions & Recommendations	18
General Recommendations for MNTE.....	18
Specific recommendations for countries yet to achieve elimination.....	18
Specific recommendations to sustain MNTE for all priority countries that achieved elimination since 1999	22
Recommendations for achieving broader tetanus prevention.....	22
Annex 1: SAGE Working Group on Maternal and Neonatal Tetanus Elimination and Broader Tetanus Prevention Membership.....	24

List of Abbreviations

ANC	Antenatal care
DHS	Demographic and Health Survey
DOV	Decade of Vaccines
EPI	Expanded programme on immunization
HIV	Human immunodeficiency virus
MCH	Maternal and child health
MICS	Multiple Indicator Cluster Survey
MNCH	Maternal, Newborn and Child Health
MNT	Maternal and neonatal tetanus
MNTE	Maternal and neonatal tetanus elimination
NT	Neonatal tetanus
PAB	Protection at birth
PICO	Population, Intervention, Comparator, Outcome
RMNCH	Reproductive, maternal, newborn, and child health
SAGE	Strategic advisory group of experts on immunization
SBA	Skilled birth attendant
SIAs	Supplementary immunization activities
Td	Tetanus and low-dose diphtheria toxoid vaccine
TTCV	Tetanus-toxoid-containing-vaccines
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
VMMC	Voluntary medical male circumcision
WHO	World Health Organization
WRA	Women of reproductive age

Executive Summary

In 1999, 59 countries with high incidence of maternal and neonatal tetanus were targeted for elimination of maternal and neonatal tetanus (MNT). Currently, 41 of the 59 of these countries have achieved elimination of MNT through routine immunization of pregnant women, clean delivery and cord care practices, together with supplementary immunization of all women of reproductive age (WRA), as and where necessary, in most countries. As of 26 September 2016, there are 18 countries that have yet to eliminate MNT and several face challenges such as lack of political commitment, insufficient funding, and insecurity. In 2015, SAGE convened a working group to examine why previous elimination target dates were missed and how to reset the agenda and comprehensively address tetanus risk across the life course.

The working group met by six teleconferences and twice in person (30 March – 1 April and 17 – 19 August, 2016) to discuss the current state of progress toward MNTE, challenges and solutions for countries yet to achieve elimination, strategies for sustaining MNTE, and strategies for broader tetanus prevention that will support the MNTE goal but also protect all other age groups against tetanus.

Tetanus prevention is achieved through immunization in all age groups besides continued clean delivery and cord care. Natural infection does not induce protective antibody response. Immunization only provides individual protection.

The working group examined strategies of countries that had successfully achieved elimination and the challenges faced by those who had failed to do so and discussed ways for overcoming these challenges. The working group also discussed strategies to sustain MNTE and the broader tetanus prevention, including the use of sero-surveys to monitor immunity gaps and reviewed evidence of the duration of protection induced by tetanus toxoid containing vaccines (TTCV) in order to define immunization schedules that would provide protection across the life course.

After examining the evidence, the working group developed recommendations for countries yet to achieve elimination, recommendations to sustain MNTE for priority countries that achieved elimination since 1999, and recommendations for achieving tetanus prevention across the life course through routine immunization programmes and, if needed, supplementary immunization campaigns.

Background

Tetanus disease

Tetanus is caused by bacterium *Clostridium tetani*. The bacterial spores generally enter through a break in the skin such as a cut or puncture wound by a contaminated object. In the presence of anaerobic (low oxygen) conditions, the spores germinate. Toxins are produced and disseminated via blood stream and lymphatic system. Toxins act at several sites within the central nervous system, including peripheral motor end plates, spinal cord, and brain, and in the sympathetic nervous system. The typical clinical manifestations of tetanus are caused when tetanus toxin interferes with release of neurotransmitters, blocking inhibitor impulses. The bacteria are commonly found in soil, dust and manure irrespective of geographical location. The incubation period varies between a few days to several weeks after tetanus bacteria enter through a break in the skin. Common signs and symptoms of tetanus include: spasms and stiffness in the jaw muscles (trismus). Tetanus diagnosis is based on physical exam, medical and immunization history, and the signs and symptoms of muscle spasms, stiffness and pain. Laboratory tests generally are not helpful for the diagnosis.

Tetanus is a medical emergency requiring hospitalization, immediate treatment with human tetanus immune globulin (TIG) or equine antitoxin if human immune globulin is not available, a tetanus toxoid booster, agents to control muscle spasm, and aggressive wound care and antibiotics. Mortality varies with access to advanced health care.

Tetanus disease burden

No good overview of number of tetanus cases worldwide is available. Surveillance systems have mainly focused on maternal and neonatal tetanus deaths, and in particular the neonatal deaths. However, existing surveillance systems in areas with well-functioning immunization programmes such as in the European Union (n=31 countries with a population of ~500 million) identify 50-100 reported cases per year. Whether these cases are a result of no vaccination or waning immunity is unknown.

Neonatal tetanus: In 1988, an estimated 780,000 deaths were attributable to neonatal tetanus. Through extensive efforts providing TTCV in routine immunization programmes targeting children and pregnant women, the estimated number of neonatal tetanus deaths had declined to 49,000 by 2013. This represents a 94% reduction in mortality during this 25 year period^{1,2} (see figure 1). There are no estimates for subsequent years. However, these remaining tetanus-related neonatal deaths each year reveal distressing health inequities, as no child should die from neonatal tetanus given the availability of a safe, effective and inexpensive vaccine.

¹ WHO/UNICEF database. http://www.who.int/immunization/diseases/MNTE_initiative/en/index7.html.

² CHERG Reports March 2015. <http://www.who.int/immunization/diseases/tetanus/Lancet-2013-Global-child-mortality.pdf>.

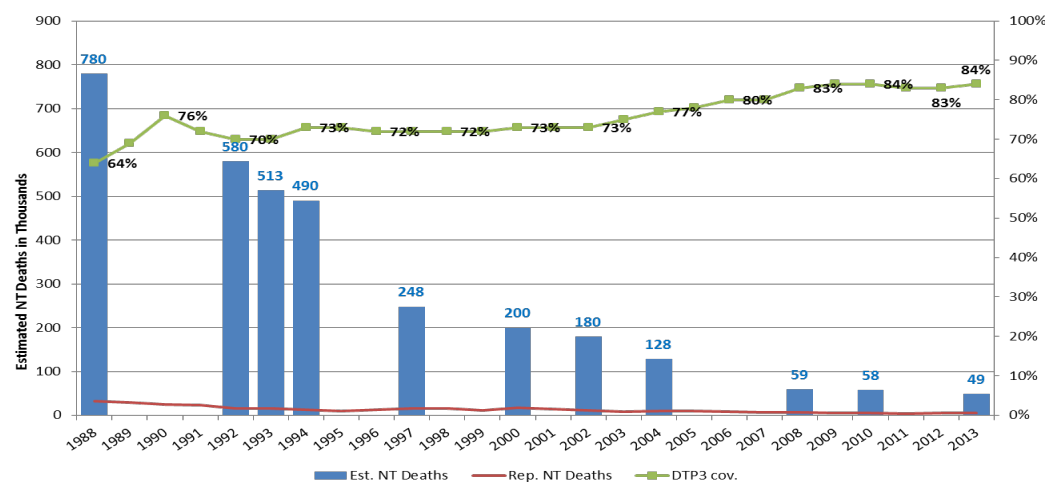


Figure 1. Trends in global estimated and reported neonatal tetanus deaths, 1988-2013 depicted on the left y axis and global estimates of DTP3 coverage in infants
Source: WHO/UNICEF database and CHERG Reports March 2015

Maternal tetanus: There are no reliable estimates of the burden of maternal tetanus, though it is generally considered to be prevalent in areas where neonatal tetanus remains endemic.

Prevention against tetanus

Clean care: Before tetanus vaccines became available in the late 1930s, protection against tetanus disease and mortality was dependent upon appropriate wound care and clean delivery and cord care practices.

Immunization: Tetanus vaccines became available in the late 1930s and were slowly introduced in childhood immunization programmes throughout the world. The scale up of TTCV in low and middle income countries began with the launch of the expanded programme on immunization (EPI) in 1974 and further reduced the number of susceptible children. Coverage worldwide for the three first doses of TTCV was estimated to 84% in 2013 (see Figure 1). The three priming doses mainly protect the first few years of life and for long-term immunity, booster doses are needed. Booster doses were recommended in the 2009 WHO position paper at 4-7 years of age, at 12-15 years of age and in early adulthood. Maternal immunization programmes were initiated in 1995 (see below). TTCV are available as monovalent TT or in combination with other antigens such as D, d, P, aP, IPV, Hep B, Hib (e.g. DTP, Td, DTPHepB, Hib, DTaP, DTaPiPVHib, DTaPiPVHibHepB).

Experience acquired from the established MNTE programme

In the late 1980s there was an increased recognition of the magnitude of neonatal tetanus deaths persisting in many countries worldwide and following a 1989 World Health Assembly resolution for all countries to eliminate NT by 1995 (later defined as reduction of NT to less than 1 case per 1,000 live births in every district in each country), routine maternal immunization with TTCV during pregnancy was introduced. In addition, supplementary immunization campaigns targeting all women of reproductive age (usually 15-49 years) have been conducted extensively.

Significant achievements but targets not fully met

The target set by the 1989 World Health Assembly resolution calling for the elimination of neonatal tetanus by 1995 was not achieved. In 1999, UNICEF, UNFPA and WHO launched a new initiative targeting 59 priority countries in which neonatal tetanus remained a significant public health problem³. Recognizing the close link between neonatal and maternal tetanus, the scope of the elimination programme was then broadened to include both maternal and neonatal tetanus. Strategies to attain MNTE include clean delivery and cord care practices, and ensuring protection at birth through immunization, including routine immunization of pregnant women during each pregnancy and immunization of all women of reproductive age (15-49 years) in high risk districts during SIAs. While surveillance for neonatal tetanus was part of the strategy, the quality of reporting of cases has remained inadequate. The global protection at birth (from tetanus) estimate that is based on TTCV coverage in pregnant women is 83% for 2015, and has been at 80% and above since 2006. By the end of 2015, over 140 million women of reproductive age had been reached by SIAs with at least two protective doses of tetanus vaccine. However, there are still an estimated 72 million women of reproductive age remaining who have not yet been targeted with SIAs for immunization with TTCV in the remaining 18 countries at risk.

As described above in addition to TTCV vaccination, strategies such as clean delivery, and cord care are important for the elimination of MNT. Evidence suggests that clean delivery practices can reduce the incidence of NT by 55-99%⁴. Skilled birth attendants (SBAs) can prevent about 2/3 of deaths among women and newborns, including tetanus⁵. Increasing institutional deliveries can also play an important role in reducing NT, provided there is adequate attention to quality of care and infection control practices in health facilities. Although evidence illustrates the efficacy of appropriate antenatal care (ANC), including immunization, and clean delivery by an SBA in reducing MNT, the least developed countries have low SBA and ANC coverage (Figures 2 and 3). Furthermore, primipara compared to multipara were found to have received fewer doses of TTCV during ANC⁶.

The application of all or most appropriate strategies has enabled 41 of the 59 priority countries initially identified for MNTE to achieve elimination as of August 2016 (Figure 4).

³ Initially 57 countries that became 59 after independence of Timor Leste and South Sudan in 2002 & 2011 respectively

⁴ "The challenges to boost ANC coverage & clean delivery and cord care to achieve MNTE in all districts." Presentation by Neelam Bhardwaj, UNFPA on March 30 to April 1, 2016.

http://www.who.int/immunization/sage/meetings/2016/october/Compilation_presentations_SAGE_WG_MNTE.pdf.

⁵ UNFPA. State of the World's Midwifery 2014. <http://www.unfpa.org/sowmy>.

⁶ Peter Bjerregaard, Robert Steinglass, DM Mutie, et. al. "Neonatal Tetanus Mortality in Coastal Kenya: A Community Survey." International Journal of Epidemiology. Vol 22, no. 1. 1993. <http://www.ncbi.nlm.nih.gov/pubmed/8449639>.

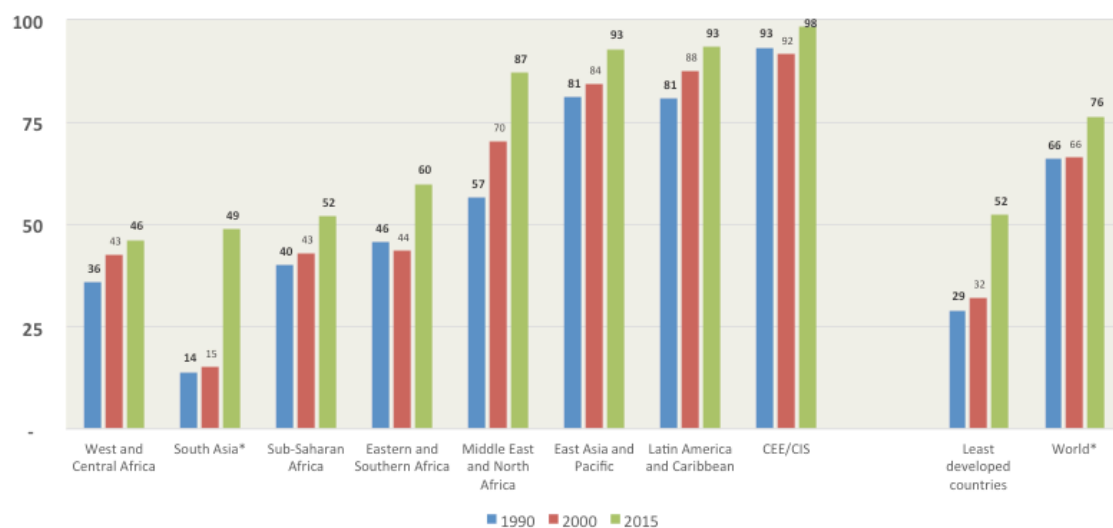


Figure 2. Percentage of births attended by skilled health personnel. Regional trends 1990, 2000, and 2015⁷. Source: UNICEF global databases 2015 based on MICS, DHS, and other nationally representative sources.

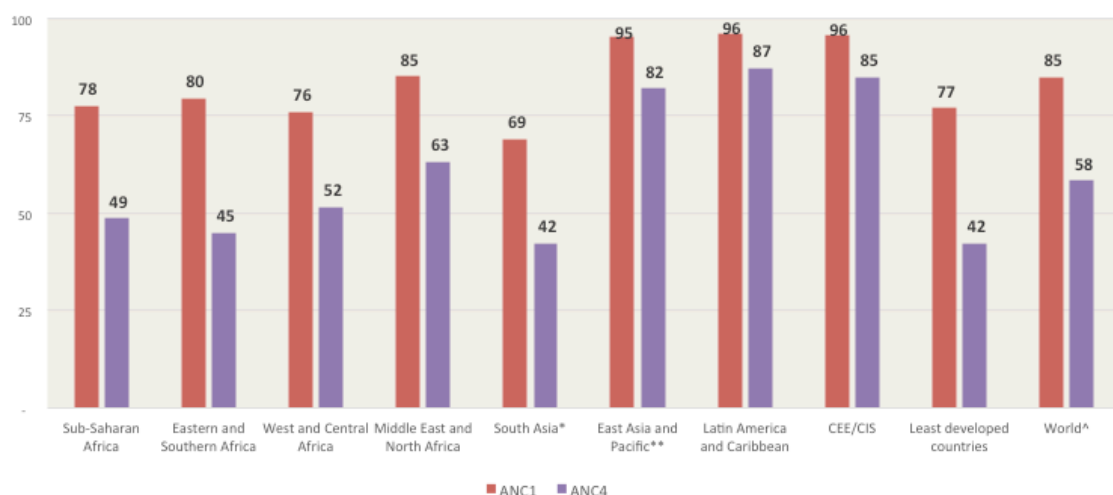


Figure 3. Percentage of women aged 15-49 years attended at least once (ANC1) during pregnancy by skilled health personnel (doctor, nurse or midwife), and percentage attended by any provider at least four times (ANC4) 2010-2015⁸. Source: UNICEF global databases 2015 based on MICS, DHS, and other nationally representative sources.

⁷1990 (1986-1997 median year 1992), 2000 (1998-2009 median year 2000) and 2015 (2010-2015, median year 2013).

*South Asia region excludes India. Global estimates are based on a subset of 103 countries, covering 76% of births in 2015. Regional estimates represent data from countries covering at least 50% of regional births.

⁸ANC1 estimate for South Asia does not include India. ANC4 estimate for East Asia and the Pacific does not include China. Estimates are based on a subset of countries with available data for the period 2010-2015. The ANC1 analysis includes 107 countries covering 85% of births worldwide, and the ANC4 analysis includes 119 countries covering 85% of births worldwide. Estimates represent data from countries covering at least 50% of regional births.

The 18 countries that remain to eliminate MNT are Afghanistan, Angola, Central African Republic, Chad, Democratic Republic of the Congo, Ethiopia, Guinea, Haiti, Kenya, Mali, Nigeria, Pakistan, Papua New Guinea, Philippines, Somalia, Sudan, South Sudan, and Yemen (see Figure 4). The risk for MNT is often restricted to few districts in most of the remaining countries as a result of the elimination activities that have been implemented over the years (see Figure 4). However, there are six countries facing challenges in achieving MNT due to insecurity: Afghanistan, Central African Republic, Mali, Nigeria, Pakistan, and Yemen. Some of these countries have also struggled to eliminate polio.

Besides the difficulty with insecurity mentioned above, MNTE targets have been repeatedly missed due to insufficient funding, ineffective communication and community engagement, ineffective integration of RMNCH and EPI platforms, weak health systems and competing priorities. Insecurity remains a major obstacle to access populations in need of vaccination. The use of compact single-dose pre-filled auto-disable injection device would permit not only trained health professionals but also community workers to provide TTCV to susceptible women living in such insecure areas. The studies conducted in several countries (Afghanistan, Burkina Faso, Ghana, Mali ⁹, Somalia, and Southern Sudan) showed that also community workers could successfully deliver vaccine using these devices outside of the cold chain to vaccinate individuals against tetanus during SIAs ^{10,11}. The use of such devices was tested and shown to be effective in TT SIAs in pilot studies in several countries that include Afghanistan, Chad, Ghana, Mali and Somalia among others. These devices would be especially useful in achieving MNTE countries such as: Afghanistan, Central African Republic, Chad, Nigeria, Pakistan, Somalia, South Sudan, Sudan, and Yemen. Forty percent of women of reproductive age, as estimated by UNICEF, in these nine countries are inaccessible to either routine or supplementary TTCV immunizations (~18 million women) ¹¹.

In order to accelerate the achievement of MNTE through SIAs in the remaining 18 countries, 98 million USD is required to conduct SIAs in high risk districts using regular injection practices and additional 50 million USD for compact single-dose pre-filled auto-disable injection devices to reach inaccessible populations in areas of insecurity. Given the current funding pledged, there is a shortfall of 87 million USD. Timely securing of funding support is essential to achieve MNTE in the remaining 18 countries.

⁹ Presentation by BASICS II for WHO TechNet Consultation March 22-25, 2003, Antalya, Turkey.

http://www.who.int/immunization/sage/meetings/2016/october/Compilation_presentations_SAGE_WG_MNTE.pdf.

¹⁰ Glenton, C., Khanna, R., Morgan, C. and Nilsen, E. S. (2013), The effects, safety and acceptability of compact, pre-filled, autodisable injection devices when delivered by lay health workers. *Trop Med Int Health*, 18: 1002–1016.

<http://onlinelibrary.wiley.com/doi/10.1111/tmi.12126/full>.

¹¹ "TT Uniject: Programmatic Needs vis-à-vis Availability." Presentation by Azhar A Raza, UNICEF on August 17, 2016. http://www.who.int/immunization/sage/meetings/2016/october/Compilation_presentations_SAGE_WG_MNTE.pdf.

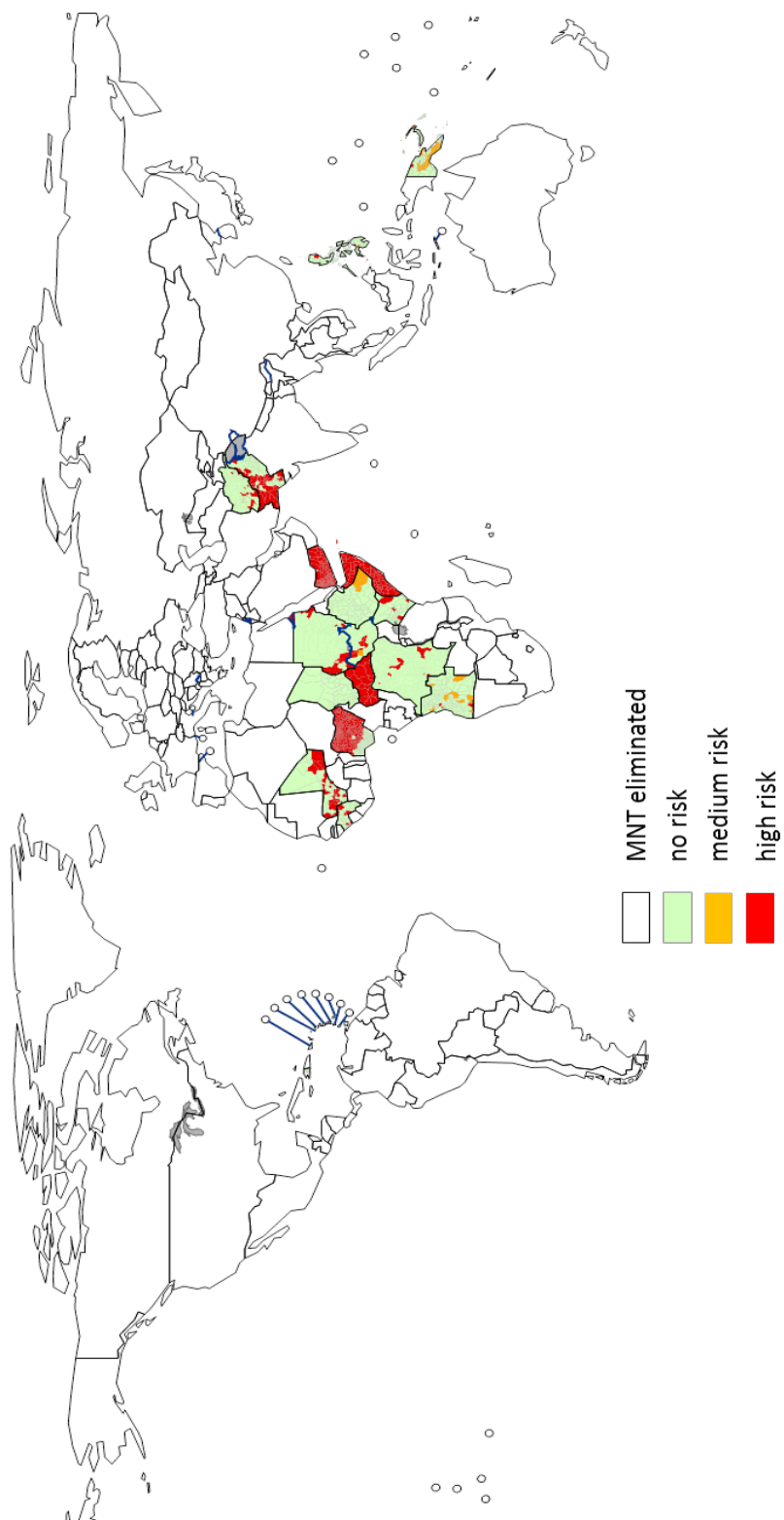


Figure 4. District MNT risk status in remaining 18 countries yet to attain elimination. Source: WHO/UNICEF database. Map production: Immunization, Vaccines, and Biologicals (IVB), World Health Organization

Factors contributing to achievement of MNTE

Many of the target countries identified in 1999 have achieved MNTE due one or several factors including: national commitment, timely availability and disbursement of resources, detailed micro-planning and quality implementation of SIAs, effective community engagement, monitoring and supervision of implementation, and integrated delivery of maternal and child health services, including clean delivery and cord care. Six¹² out of 41 validated countries achieved elimination without any supplementary vaccination campaigns, and basically relied on efforts to strengthen the health system.

There are several country examples of successfully overcoming challenges to eliminate MNT. India was able to achieve MNTE in 2015. Following the recognition of a significant burden of NT (150,000 to 200,000 estimated cases per year in the 1980s) in India, the country introduced TTCV immunization for pregnant women using ANC in the 1980s. In the last decade, India also created demand through conditional cash transfers for institutional delivery, strengthened the supply side, and conducted an intensive behavior change communication campaign, including the use of community mobilizers to promote clean cord care practices. Pregnant women are currently given two doses of TTCV four weeks apart. If the next pregnancy is within three years, one booster dose of TT is provided. India has introduced TTCV during infancy and childhood, including three primary doses of DTP at 6, 10, and 14 weeks, booster doses at 16-24 months, at 5-6 years, at 10 and 16 years. India also used TT SIAs among women of reproductive age in a few selected high risk areas¹³.

Indonesia is another example of a country that has achieved MNTE. Besides maternal immunization programme Indonesia introduced tetanus immunization using a school-based platform. In 1979, two doses of TT for pregnant women were introduced, and school immunization was introduced in the 1980s. The TTCV vaccination schedule in Indonesia is the primary series of TTCV in infancy, DTP4 at 18 months, DT in first grade of school, and Td in the second grade and third grades. There is a plan to postpone the third grade dose until fifth grade to prolong protection. This schedule is expected to provide protection against tetanus for approximately 25 years, which is most of the reproductive age of women. School based immunization against tetanus and diphtheria is routinely conducted nationwide every November in all public and private schools. Additionally, short term TT SIAs have been conducted in high risk districts for maternal and neonatal tetanus. Indonesia recently introduced universal health coverage for facility based delivery in 2015. The country has also focused on improving clean delivery and cord care practice and improving sensitivity of NT surveillance¹⁴.

¹²China, Eritrea, Namibia, Rwanda, South Africa, Zimbabwe

¹³ Presentation on "India: Achieving MNT Elimination – Health Systems Approach" by Rakesh Kumar of the Government of India, 30 March to 1 April 2016.

http://www.who.int/immunization/sage/meetings/2016/october/Compilation_presentations_SAGE_WG_MNTE.pdf.

¹⁴ Presentation on "Critical operational challenges to achieving at least 80% protection at birth from MNT in high risk districts" by Jane Soepardi, 30 March to 1 April 2016.

http://www.who.int/immunization/sage/meetings/2016/october/Compilation_presentations_SAGE_WG_MNTE.pdf.

These country examples illustrate that MNT can be successfully eliminated with appropriate strategies for immunization, clean delivery and cord care, as well as NT surveillance, combined with political commitment and resource allocation. Furthermore, Indonesia has shown that a school-based immunization platform can be an effective tool for certain countries to deliver TTCV for both sexes and provide high levels of long-lasting population immunity to tetanus. A 2009 WHO review of Indonesia, Malaysia, Sri Lanka, Syria, and Tunisia¹⁵, noted several factors that contributed to successful school vaccination programmes, including high enrollment of both sexes, a strong primary health care system, strong central government support for supplies and equipment, collaboration between the Ministry of Health and the Ministry of Education, appropriate guidelines and training, cooperation of school and health care staff, and trust in the public health and education systems¹⁶. Countries that have achieved MNT provide lessons on the important factors for success and potential strategies that can be used.

Sustaining MNT

The working group reviewed a draft guide for sustaining MNT in countries that have achieved MNT. The guide proposes review of performance of tetanus elimination strategies in each district annually. This annual review exercise should be a joint exercise by the immunization programme, Maternal, Newborn and Child Health (MNCH), and surveillance managers together with partner representatives. The objectives of this review are: (i) to identify and classify districts that could potentially revert back to at risk for MNT; (ii) to select and tailor relevant corrective strategies and interventions to sustain MNT in the short, and longer term; and (iii) to use this review as an opportunity to improve EPI and MNCH programmes with particular attention to optimizing the use of ANC and immunization platforms. The review of district performance aims at classifying districts' risk status for MNT that will guide the implementation of the corrective action to maintain the districts' elimination status.

The decision on corrective measures and immunization, ANC, SBA and NT surveillance approaches will have to take into account the country policy/strategy and local context, the district classification in "low risk" or "at risk" (medium and high risk) and specificities (main reasons for the low TT protection, assessing if it is a district wide or health facility catchment area specific issue) and the feasibility of implementing the corrective measures.

The Working Group's review of a draft UNICEF/WHO guidelines concluded that the draft document was complex and needed to be presented in two parts with one part focusing on the policy issues to sustain MNT and the second part focusing on the operationalization of the required corrective activities to sustain elimination. There may also be a need for pilot testing or public consultation of the guidelines. The maternal newborn health group may

¹⁵ School-based immunization

http://www.who.int/immunization/programmes_systems/policies_strategies/school_based_immunization/en/.

¹⁶ Presentation of "New' Vaccination Platforms and Opportunities for TTCV Boosters" by Tracey Goodman of WHO, 18 August 2016.

http://www.who.int/immunization/sage/meetings/2016/october/Compilation_presentations_SAGE_WG_MNT.pdf.

also provide feedback. The emphasis on district level risk assessment is important, and it is important to sustain MNTE in a way that broadens the prevention of tetanus. Opportunities that include second year of life, adolescence, and school-based vaccination should be maximally utilized.

Sero-surveys could be used post-elimination to supplement the data from the reviews of district data and provide information immunity profiles in women of child bearing age and identify subpopulations with immunity gaps for corrective actions. However, in an ideal situation sero-surveys should aim to conduct comprehensive surveys that provide information of immunity profiles in both genders and all age groups, generate evidence for the need to introduce or scale up the coverage with booster doses, and identify areas and age groups for corrective action, as discussed later in this report.

Community engagement and effective communication are essential to achieving and sustaining MNTE. A review of systematic reviews was conducted to assess the impact of community-based interventions targeted at preventing MNT morbidity and mortality. The PICO (Population, Intervention, Comparator, Outcome) question was “What is the impact of community-based interventions on pregnant women and/or neonates compared to no intervention or alternative interventions in preventing maternal and neonatal deaths or increasing maternal immunization coverage?” The review yielded six systematic review articles. Of these, 3 assessed the impact of community based interventions on cause-specific neonatal mortality due to tetanus and 4 assessed the proportion of women with tetanus protection at birth. The review confirms that community-based interventions in low and middle-income settings are a valid strategy to decrease maternal and neonatal mortality and improve health outcomes in mothers and infants. However, the retrieved reviews provided little specific information on the effect of these interventions on reducing maternal and neonatal tetanus related mortality and little information on the impact on maternal tetanus immunization status.

In addition to improving immunization coverage, clean delivery and cord care practices, it is important to strengthen surveillance and reporting of neonatal tetanus, as part of more comprehensive surveillance for tetanus, and ensure that corrective action is taken when a neonatal tetanus case is documented.

Broader Tetanus Prevention

The working group also considered strategies for broader tetanus prevention, including a re-examination of routine immunization schedules. Strengthening implementation of routine immunization schedules will help sustain MNTE and prevent tetanus in other groups, including adolescents and adults, particularly males who currently do not receive the full complement of booster doses in many countries.

The current WHO position paper recommends three primary doses of DTP in infancy, a booster dose of dT at 4-7 years of age, a booster dose of dT at 12-15 years of age, and a

booster dose of dT in early adulthood¹⁷. However, 49 of the 194 WHO Member States have not included childhood and adolescent booster doses in their national immunization schedules. In addition, when booster TTCV doses are included in the national schedules, implementation and monitoring of coverage with booster doses have sometimes not been a priority. In some WHO regions more than 80% of the population lives in countries where diphtheria vaccination beyond 5-6 years of age is not included in the national schedule.

Long term immunity

A review of published systematic reviews was conducted to examine vaccination schedules used for preventing tetanus and duration of vaccine-induced protection. The PICO (Population, Intervention, Comparator, Outcome) question was “What is the duration of continued protection (efficacy, effectiveness or immunity) against tetanus conveyed by a specific schedule of TTCV vaccination?” No publication on the continued duration of protection (>5 years after immunization) conferred by specific schedules of tetanus containing vaccines could be retrieved. However, sero-surveillance data were presented from multiple countries with different vaccination schedules and supported the understanding that several booster doses of TTCV after the primary infant series are necessary for life-long protection¹⁸.

Population immunity following routine immunization and SIAs

Serological studies and case reporting in the European Union (n = 31 countries, population ~500 million) suggest that women of older age groups are most susceptible to tetanus but significant immunity gaps have also been identified in population groups refraining from vaccination due to religion or vaccine hesitancy and migrants from other parts of the world upon arrival in Europe¹⁹.

Newer serologic data and case reports of tetanus from Africa illustrate an immunity gap in adult males as compared to females since females are primarily targeted for adolescent and adult vaccination due to MNT risk and many countries have not included childhood and adolescent booster doses in their national immunization schedules despite the already long standing WHO recommendations²⁰. Among the 11.6 million Voluntary Medical Male Circumcisions (VMMC) performed under a programme for HIV prevention from 2008 to 2016, fifteen cases of tetanus were reported during 2012 to 2016, illustrating an immunity gap in adult males²¹. Routine reporting of tetanus cases is extremely inadequate in large parts of the world.

¹⁷WHO. Tetanus vaccine: WHO position paper. Weekly Epidemiological Record, 2006. 20:81, 197-208.

¹⁸R Borrow, P Balmer, and MH Roper. The immunological basis for immunization series. Module 3: Tetanus Update 2006. http://apps.who.int/iris/bitstream/10665/43687/1/9789241595551_eng.pdf.

¹⁹Steens A, Mollema L, Berbeers GAM, van Gageldonk PG, van der Klis FR, de Melker HE. High tetanus antitoxin antibody concentrations in the Netherlands: a seroepidemiological study. Vaccine 2010;28:7803-9. And the ECDC Annual report 2015. <https://www.ncbi.nlm.nih.gov/pubmed/20875496>.

²⁰Presentation on “Tetanus serosurveys,” by Heather Scobie and Alison Ridpath of CDC, 17-19 August 2016.

²¹Presentation on “HIV prevention through voluntary medical male circumcision and TTCV gaps for males,” by Liz Miller of Public Health England and Julia Samuelson of WHO Department of HIV/AIDS, 18 August 2016. http://www.who.int/immunization/sage/meetings/2016/october/Compilation_presentations_SAGE_WG_MNTE.pdf.

Following the first reports of tetanus in newly circumcised men, the WHO HIV/AIDS Department examined hospital studies of non-neonatal tetanus in Sub-Saharan Africa published from 2003-2014 and found that 71% of the hospitalized tetanus cases were in males²². Recent data from sero-surveys conducted in Kenya, Tanzania, and Mozambique reveal disproportionately high immunity gaps in males 15 years and older (Figure 5). There is a clear difference in immunologic protection against tetanus between adult men and women since adult males do not receive booster doses of TTCV in many countries, whereas adult females are more likely to receive booster doses, either during supplementary immunization activities (SIA) or during pregnancy.

Furthermore, these data illustrate declining sero-protection rates in older children (5-15 years) in the absence of booster doses. Since early 2000, the national immunization programme in Mozambique has included two TTCV booster doses in first and second grades of school to boys and girls while Kenya and Tanzania do not. In the sero-survey Mozambique has high rates of seroprotection among children aged 5-14 while Kenya and Tanzania have lower rates of seroprotection²³.

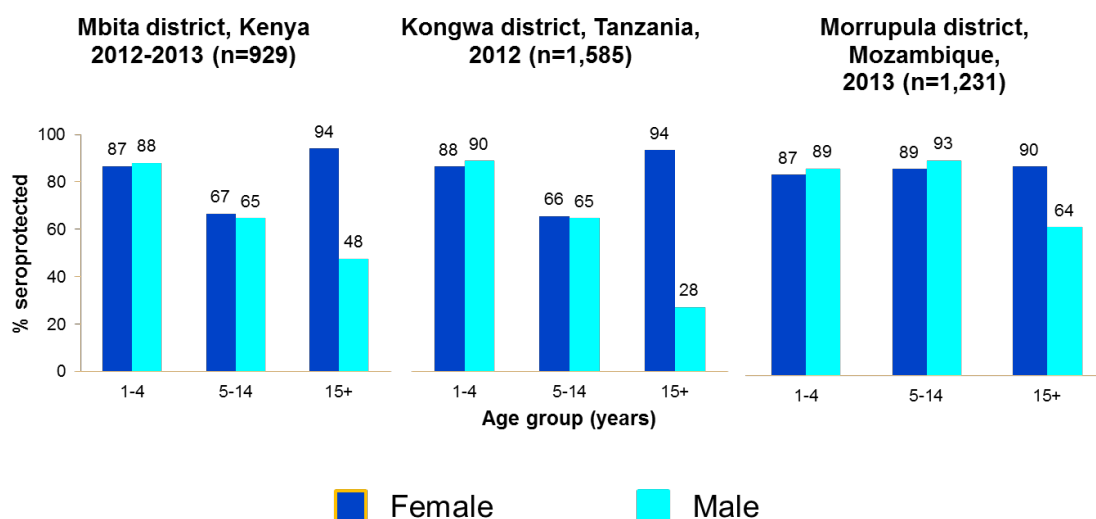


Figure 5: Results of percentage of sero-protected individuals at district level in three eastern and southern African countries. Source: Scobie et al, in press

Evidence shows need for improving coverage for primary doses of TTCV

The WHO UNICEF Estimates for National Immunization Coverage (WUENIC) show a global average coverage of DTP3 of 86% in 2015. Sero-surveys conducted in Eastern and Southern African countries support the JRF results that 85-90%, irrespective of gender, were shown to have protective levels of tetanus antibodies in the age group 1-4 years. Only

²² Dalal S, Samuelson J, Reed J, Yakubu A, Ncube B, Baggaley R. Tetanus disease and deaths in men reveal need for vaccination. *Bulletin of the World Health Organization*. 2016;94(8):613-621. doi:10.2471/BLT.15.166777. <https://www.ncbi.nlm.nih.gov/pubmed/27516639>.

²³ Tetanus immunity gaps among adult men in Kenya, Tanzania, and Mozambique revealed by multiplex serologic surveillance by Scobie et al., In press, *American Journal of Tropical Medicine & Hygiene*.

if coverage reaches close to 100% for the primary series can elimination of all tetanus including MNT be achieved. The primary series is the basis for life long immunity. Noting the historical low coverage with the primary series of TTCV in many countries, all opportunities for providing primary series for those who missed these doses in infancy should be fully utilized.

Evidence shows need for providing booster doses of TTCV

A 2nd year of life booster is recommended for pertussis and diphtheria, and 2009 serologic data from United Kingdom showed that introducing a TTCV booster in the 2nd year of life increases tetanus protection lasting until school-entry compared to the three-dose primary series only²⁴. Serologic data from Kenya, Tanzania and Mali supported the need for a TTCV booster at school-entry related to substantial drop in sero-protection at ≥5 years of age²⁵. Robust immunity across age groups and persisting 20–30 years after the last vaccination was evident from serologic data related to schedules containing six total TTCV doses in the Netherlands (3, 4, 5 and 11 months; 4 and 9 years), Australia (2, 4, 6 and 18 months; 4 and 10–15 years), and England (2, 3 and 4 months; 12 months [Hib-Men C-TT conjugate]; 3.5–5 years and 13–18 years).

Opportunities for platforms to be used for booster doses

There are several platforms that provide opportunities to immunize with TTCV booster doses, including the second year of life, school-based vaccination, pre-adolescent and adolescent vaccination:

Opportunities for integration of TTCV boosters will differ among countries¹⁶. The second year of life provides a platform for vaccination against several diseases including pertussis, measles, and meningococcal A conjugate vaccines. The pre-adolescent and adolescent vaccination platform includes HPV vaccination. Introduction of tetanus toxoid-conjugate vaccines where TT vaccine is used as a carrier protein, including meningococcal group A (MenAfriVac), meningococcal group C (Men-C), *Haemophilus influenzae* type b (Hib) represent another possible opportunity for a boost in population immunity to tetanus. Increased tetanus sero-protection has been shown in affected age cohorts following Hib/Men-C routine introduction in England, a Men-C catch-up campaign in the Netherlands, and MenAfriVac catch-up campaign in Mali²⁵.

Improved surveillance for tetanus cases needed

It was mentioned already in the background that many countries in the world do not have adequate surveillance for tetanus cases, including neonatal tetanus. As with other diseases

²⁴ Wagner KS, White JM, Andrews NJ, Borrow R, Stanford E, Newton E, et al. Immunity to tetanus and diphtheria in the UK in 2009. *Vaccine*. 2012;30:7111–7. <http://www.ncbi.nlm.nih.gov/pubmed/23022148>.

²⁵ Basta NE, Borrow R, Berthe A, et al. Higher Tetanus Toxoid Immunity 2 Years After PsA-TT Introduction in Mali. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2015;61(Suppl 5):S578-S585. <http://www.ncbi.nlm.nih.gov/pubmed/26553691>.

targeted for elimination, due attention should be paid to improving surveillance and reporting of tetanus cases as part of national integrated disease surveillance efforts.

The working group noted that the neonatal tetanus elimination rate of 1 case per 1000 live births is high compared to other disease targets that often are in the range of 1 case per 100,000 or even lower. However, it would be difficult to change the target so late in the MNTE process so it was viewed better to find ways to capitalize on the current elimination environment. It was also noted that in the absence of high quality surveillance, incidence rates below this level would be difficult to measure. Currently, lot quality assurance surveys in the worst performing districts are used for validating that the threshold of less than 1 case per 1000 live births is met. Surveys to detect lower thresholds would be extremely resource intensive.

Using NT surveillance to monitor MNTE can be a powerful tool and can reveal health system failures. NT shows failure to reach women with TTCV, failure to provide service for clean delivery, and failure to provide adequate clinical services when mothers or newborns are affected by tetanus. NT finds the vulnerable, such as women that have no ANC and no TTCV vaccination, women who attend ANC but do not receive TT vaccination, and women who deliver at a health facility or with a midwife but the practices are unclean. Surveillance has a critical role to reveal causes of MNT and assist in finding practical solutions.

Community based NT surveillance can help to identify NT cases that die in the community and may not be reported to health care workers. However, it requires an extensive network, training, supervision, and investigation. An option may be to do community sensitization so the community will report cases to the health center and the health center can investigate or obtain district level support.

Improving NT surveillance may require integration with vital event registration and reporting, including neonatal deaths, that can then be investigated. This needs to be seen in the context of child survival, not only neonatal tetanus. A feasible imperfect solution is better than a perfect unrealistic option. It is important to have realistic expectations for NT surveillance. Rather than finding every last case, finding a few cases can provide important information. There is also no background rate like with AFP surveillance so it can be difficult to measure surveillance quality.

NT surveillance needs to play a relevant role to identify continued risk areas and corrective actions after validation. Surveillance needs to be supplemented by other relevant data on immunization, ANC, delivery, and cord care practices. The aim is to comprehensively understand and assess systems aspects. There are feasible and practical actions that can be taken to improve NT surveillance. The investigation of one NT case can provide information about the needs of the community.

Maternal deaths audit can also provide useful information on maternal tetanus.

Monitoring immunity gaps

Sero-surveys may play an important role in assessing immunity gaps across all age groups in both genders to inform corrective actions (e.g., catch-up campaigns of groups shown to have immunity gaps or introduction of booster doses). Data from sero-surveys could also be used along with other data in assessing risks and taking required corrective actions to sustain MNTE.

Sero-surveys may give a more accurate measure of tetanus immunity than administrative coverage or surveys. One study assessed administrative DTP3 coverage, surveyed DTP3 coverage, and sero-protection among 12-23 month old children in three districts in Ethiopia and found that serology showed lower percentages of protected individuals than administrative coverage data but higher percentages than coverage survey data, probably due to faulty maternal recall and incomplete documentation of vaccination records (Figure 6)²⁶. Studies in Burundi, Central African Republic, and Cambodia comparing protection at birth (PAB) to sero-protection in women of reproductive age have also shown differences in the two measures^{27,28,29}. For example, in Cambodia, sero-protection in parous women 15-39 years of age was 97% while PAB using coverage data was estimated to be 83%²⁹. In some cases, PAB may underestimate the percentage of women protected when compared to serology results due to residual immunity from TTCV in infancy, booster doses given outside routine immunization services, and misclassification when using the PAB method due to lack of documentation and recall bias.

Furthermore, tetanus serology could be performed using a multiplex testing platform, which would allow for the testing of multiple antigens across public health programmes to reduce the cost. However, the choice of laboratory test used is important for validity of sero-survey results.

In-vitro tests exist that have been validated as accurate at the accepted standard for sero-protection (≤ 0.01 IU/ml based on *in-vivo* neutralization), but they are not commercially available (e.g., competition ELISA, double-antigen ELISA, toxin-binding inhibition, multiplex bead assay). Indirect ELISAs are not accurate < 0.2 IU/ml because they detect both neutralizing and non-neutralizing antibodies, requiring use of a higher cutoff (e.g., 0.2 IU/ml)³⁰. Commercial options for indirect ELISA exist, but none has been validated against

²⁶Travassos MA, Beyene B, Adam Z, Campbell JD, Mulholland N, Diarra SS, et al. (2016) Immunization Coverage Surveys and Linked Biomarker Serosurveys in Three Regions in Ethiopia. PLoS ONE 11(3): e0149970. <http://www.ncbi.nlm.nih.gov/pubmed/26934372>.

²⁷WHO. Expanded programme on immunization –estimating tetanus protection of women by serosurvey. Weekly Epidemiological Record, 1996, 71(16): 117-24. <http://www.ncbi.nlm.nih.gov/pubmed/8775796>.

²⁸Deming MS, ROUNGOU J-B, Kristiansen M, et al. Tetanus toxoid coverage as an indicator of serological protection against neonatal tetanus. *Bulletin of the World Health Organization*. 2002;80(9):696-703. <http://www.ncbi.nlm.nih.gov/pubmed/12378286>.

²⁹Scobie HM, Mao B, Buth S, Wannemuehler KA, Sørensen C, Kannarath C, Jenks MH, Moss DM, Priest JW, Soeung SC, Deming MS, Lammie PJ, Gregory CJ. 2016. Tetanus immunity among women aged 15 to 39 years in Cambodia: a national population-based serosurvey, 2012. *Clin Vaccine Immunol* 23:546–554.10.1128/CVI.00052-16. <https://www.ncbi.nlm.nih.gov/pubmed/27053629>.

³⁰Matos D.C.S., Marcovitz R., Cabello P.H., Georgini R.A., Sakauchi D., Leite L.L. Immunogenicity test of tetanus component in adsorbed vaccines by Toxin Binding inhibition test. *Mem Inst Oswaldo Cruz*.2002;97:909–913. <https://www.ncbi.nlm.nih.gov/pubmed/12386721>.

in vivo or *in vitro* tests accurate at the 0.01 IU/ml threshold for sero-protection. In addition to concerns of misclassification bias related to using higher cutoff for indirect ELISA, performance of individual tests appears variable with some commercial tests having documented issues with accuracy and precision³¹.

WHO could play a crucial role in establishing a tetanus laboratory network supporting diagnostics and sero-surveys.

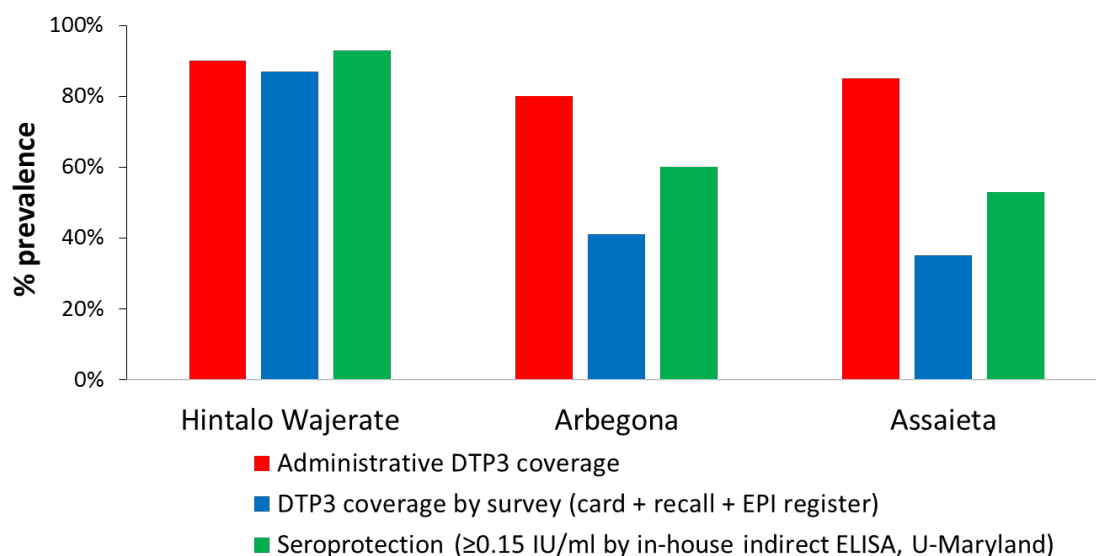


Figure 6. DTP3 coverage by administrative data and survey and tetanus seroprotection among 12-23 month old children in three districts in Ethiopia, 2013. Data source: MA Travassos, B Beyene, Z Adam, JD Campbell, N Mulholland, SS Diarra, et al. Immunization coverage surveys and linked biomarker sero-surveys in three regions in Ethiopia. PLoS ONE 2016; 11(3): e0149970.

Proposed revision of the WHO Tetanus position paper

The Working Group agrees on the need to revise the tetanus position paper with the understanding of the need for a clear decision from SAGE if any recommendation from the position paper needs to be changed or if any new recommendations are added. The Working Group would need to present SAGE with necessary evidence if any recommendation needs to be changed.

The justification for updating the position paper is based on:

³¹ Van Hoeven KH, Dale C, Foster P, Body B. Comparison of Three Enzyme-Linked Immunosorbent Assays for Detection of Immunoglobulin G Antibodies to Tetanus Toxoid with Reference Standards and the Impact on Clinical Practice. *Clinical and Vaccine Immunology : CVI*. 2008;15(12):1751-1754. doi:10.1128/CVI.00254-08. <https://www.ncbi.nlm.nih.gov/pubmed/18845832>.

- Need to clarify for countries what type of vaccine they can use for different booster doses (options for TTCVs including DTP, DT, Td, pentavalent, hexavalent, etc.; no clarity on age at which Td can be used)
- A booster dose during the second year of life is currently not mentioned while both diphtheria and pertussis are recommended at this age
- Current age range recommended for administration of booster doses do not correspond to opportunity platforms as, for example, the adolescent booster
- Provision for catch up in older children, adolescents and adults if desired schedule not met during childhood
- The technical contents in the tetanus, diphtheria, and pertussis papers need to be harmonized.

Conclusions & Recommendations

Based on its review of the evidence, the WG concluded that the recurrent failure to meet MNTE targets was a reminder of persisting inequities in access to health services. The review also exposed immunity gaps in older age groups, especially among males because of focusing solely on maternal and neonatal tetanus.

The working group proposes the following draft recommendations for consideration by SAGE.

General Recommendations for MNTE

- Countries, international organizations and development agencies should consider prioritizing the implementation of all adopted strategies to achieve and maintain MNTE, including routine immunization of pregnant women, routine antenatal care (ANC), clean delivery and cord care and surveillance of MNT cases
- Achievement and maintenance of MNTE should be seen as a key indicator of universal health coverage since the disease mainly affects the most underserved and marginalized populations.
- There should be greater involvement and oversight by the WHO Regional Offices and regional immunization technical advisory groups in monitoring progress and ensuring that the global goal of MNTE is achieved, especially in the WHO regions with countries yet to achieve elimination. The regional immunization technical advisory groups should play an important role in advocating for the actions required from countries and partners especially WHO, UNICEF and UNFPA.

Specific recommendations for countries yet to achieve elimination

- Countries yet to achieve MNTE should establish/update and implement their operational plans to meet required timelines as indicated in Table 1. MNTE by 2020 to coincide with the end of the Decade of Vaccines (DOV) is feasible if timely availability of financial resources and innovative technologies (injection devices) is made available to reach the most marginalized.
- Countries should reinforce surveillance for MNT to assure accurate measurement of progress towards MNTE.
- UNICEF, UNFPA, and WHO should support countries in securing the necessary resources to implement their national elimination plans, including for procuring vaccines and for covering operational costs for SIAs.
- UNICEF, UNFPA, and WHO should make all efforts to secure timely supply of the available WHO pre-qualified tetanus toxoid vaccine in compact single-dose pre-filled auto-disable injection devices to facilitate vaccination of inaccessible populations by community workers.

- Should the supply of TT vaccine in this latter presentation be less than expected, a clear plan for prioritizing and allocating available doses should be established.

UNICEF, UNFPA, and WHO should urgently develop an MNTE investment case and resource mobilization strategy to secure funding support from potential donors, as predictable and timely resources are needed to fund operational costs of TTCV SIAs, compact one dose pre-filled auto-disable injection devices and validation surveys in the remaining 18 countries, if the 2020 elimination timeline is to be met.

Table 1. Prospect toward attainment of MNTE for the remaining 18 countries

Country category and definition	List of countries in this category	Required action	Proposed Timelines
Countries at lower risk and likely to attain MNTE by 2018 – <ul style="list-style-type: none"> Funds available for completion of all planned MNTE activities 	Angola, Chad, DRC, Ethiopia, Guinea, Haiti, Kenya, Philippines, South Sudan	Conduct SIAs for WRA in targeted high risk areas with close monitoring to assure quality	By mid-2017
		Strengthen routine delivery of TTCV to designated target groups using all opportunities through the life course approach.	By end-2017
		Validation of elimination	By mid-2018
		Development and implementation of sustainability plan	By end-2018
		Advocacy to secure funding (domestic & donor) to conduct TTCV SIAs in high risk areas	By end-2016
Countries at moderate risk and likely to attain MNTE by 2019 – <ul style="list-style-type: none"> Most funds available Relatively large proportion of WRA still to reach with quality SIAs Low to medium level of insecurity 	Papua New Guinea, Somalia, Sudan	Strengthen routine delivery of TTCV to designated target groups using all opportunities through the life course approach	By mid-2018
		Improve access to TTCV with the compact single-dose pre-filled auto-disable injection devices	By mid-2018
		Complete SIAs for WRA in targeted high risk areas with close monitoring to assure quality; use lessons learnt from experiences with polio vaccination in conflict affected areas	By end-2018
		Validation of elimination	By mid-2019
		Development and implementation of sustainability plan	By end of 2019

Country category and definition	List of countries in this category	Required action	Proposed Timelines
Countries at substantial risk and likely to attain MNTE by 2020 -- <ul style="list-style-type: none"> • Most funds not yet available • Existing substantial level of insecurity including active conflict • Weak health systems with serious access issues with relatively large proportion of WRA still to reach with quality SIAs • Other public health emergencies including polio 	Afghanistan, Central African Republic, Mali, Nigeria, Pakistan, Yemen	Enhance advocacy to secure funding (domestic & donor) for conducting TTCV SIAs for WRA in high risk areas	By end of 2017
		Strengthen routine delivery of TTCV to designated target groups using all opportunities through the life course approach.	By end-2018
		Provide TT in compact single-dose pre-filled auto-disable injection devices to improve and enhance access to TTCV	By end-2018
		Conduct SIAs with close monitoring to assure quality in all high risk areas; use lessons from polio vaccination in areas of conflict.	By end-2020
		Validation of elimination	By mid-2021
		Development and implementation of sustainability plan	By 2021

Specific recommendations to sustain MNTE for all priority countries that achieved elimination since 1999

- UNICEF, UNFPA and WHO should work with countries to generate and sustain political interest in the continuing elimination of MNT to guard against complacency once a country has been declared to have eliminated the disease.
- All immunization programmes should review and adjust their routine immunization schedules to ensure tetanus protection over the life course for all members of the population. All countries should also scale up and sustain the coverage with clean delivery and improve clean cord care practices.
- Annual monitoring of MCH, Surveillance and EPI district performance through joint desk review of core³² and surrogate³³. MNT risk indicators is a useful and appropriate method to identify high risk districts and monitor potential MNT risk. Findings should be used to implement corrective measures for immunization and MCH services.
- TT campaigns should be conducted in the districts identified as high risk, based on core and surrogate risk indicators to fill immunity gaps.
- Steps should be taken to improve the quality of monitoring, case investigation, and reporting of tetanus cases as part of broader process; these data, rather than other surrogates, should eventually be the mechanism for monitoring sustained MNTE

Recommendations for achieving broader tetanus prevention

- The booster dose schedule should be adjusted to include three booster doses, giving a total of six doses to achieve protection throughout reproductive age, probably lifelong protection. These should be given preferably during the second year of life, between 4-7 years of age, and between 9-15 years of age. Ideally there should be at least a 4-5 year interval between doses. Some countries will require technical and programme guidance to smoothly transition to these new schedules, and to establish or utilize existing platforms to offer a package of vaccination along with other health services. Further, booster doses late in life may be needed due to waning immunity.
- WHO should re-emphasize the previous recommendations³⁴ on the number of doses needed in pregnant women and clarify that pregnant women are protected when they have six documented doses (by card, immunization registry and/or history) during the time of reproductive age in order to avoid unnecessary repeat vaccinations for protection during pregnancies. A standard algorithm for determining tetanus protection based on vaccination history and expected duration

³² TT2+ coverage, Skilled birth attendance coverage, neonatal tetanus rate per 1000 live births

³³ ANC coverage, DTP1 & DTP3 immunization coverage, and percentage of population urban vs. rural

³⁴ WHO. Tetanus vaccine: WHO position paper. Weekly epidemiological record, 2006. 20:81, 197-208. http://www.who.int/immunization/policy/position_papers/tetanus/en/.

of protection should be employed to determine whether a dose is needed in the current pregnancy.

- Available sero-survey data and disease burden show declining sero-protection with increasing age and shift in ages of cases in the absence of booster doses. These data, as well as recent tetanus cases in the Voluntary Medical Male Circumcision programme, highlight the immunity gap in both females and males in different parts of the world. Updated WHO recommendations should reinforce the need for booster doses for both males and females across the life course and opportunistic catch up immunization, especially among males and the elderly. A booster dose is needed in all when exposed to specific risks.
- WHO should re-emphasize and track adoption of the recommendation that age appropriate combinations of tetanus and diphtheria toxoids should be used to promote and sustain diphtheria immunity across the life course and for both sexes and should clarify that tetanus antigen combined with low-dose diphtheria antigen (Td) is the preferred programme option for children who are 4 years of age and older.
- The use of sero-surveys to validate assessment of risk from other data sources should be considered to guide vaccination strategies, especially in high risk districts. Close attention should be paid to sampling strategies and laboratory methods to ensure that results are valid and interpretable.
- WHO should consider establishing reference laboratories and reference serum panels to support standardization and quality assurance of the laboratory methods used in sero-surveys.
- WHO should also provide guidance on sampling methods; sample collection and testing; and analysis, interpretation and use of sero-survey data.
- Achieving and sustaining tetanus elimination in every district is a signal of a country's ability to universally and equitably reach its underserved populations.

Annex 1: SAGE Working Group on Maternal and Neonatal Tetanus Elimination and Broader Tetanus Prevention Membership

SAGE members

- Kari Johansen (Chair of Working Group), Expert in Vaccine Surveillance and Response Support Unit, European Centre for Disease Prevention and Control, Sweden.
- Jaleela Sayed Jawad, Head of the immunization group, Ministry of Health, Kingdom of Bahrain.
- Charles Wiysonge, Deputy Director, Centre for Evidence-based Health Care and Professor in Community Health, Stellenbosch University, South Africa.

Experts

- Bradford Gessner, Scientific Director, Agence de Médecine Preventive, France
- Ardi Kaptiningsih, previously served as Regional Adviser, Making Pregnancy Safer, Women and Reproductive Health, WPRO, Philippines
- Rakesh Kumar, Joint Secretary and Director, Ministry of Health & Family Welfare, India
- Elizabeth Mason, previously served as Director of the Department of Maternal, Newborn, Child and Adolescent Health, WHO, Switzerland
- Elizabeth Miller (SAGE member from 2007-2013), Consultant Epidemiologist, Immunisation Department, Health Protection Agency, Centre for Infections, United Kingdom
- Tony Nelson, Clinical Professional Consultant, Department of Paediatrics, The Chinese University of Hong Kong
- Alexis Ntabona, Consultant for ExpandNET, Democratic Republic of the Congo
- Robert Steinglass, Director Immunization Center, John Snow, Inc., USA

WHO Secretariat

- Neelam Bhardwaj (UNFPA)
- Azhar Abid Raza (UNICEF)
- Ahmadu Yakubu (WHO)

Tetanus vaccine

WHO position paper

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO is issuing a series of regularly updated position papers on vaccines and vaccine combinations against diseases that have an international public health impact. These papers, which are concerned primarily with the use of vaccines in large-scale immunization programmes, summarize essential background information on the respective diseases and vaccines and conclude with the current WHO position concerning their use in the global context. The papers have been reviewed by a number of experts within and outside WHO and, since April 2006, are reviewed and endorsed by the WHO immunization Strategic Advisory Group of Experts. They are designed for use mainly by national public health officials and immunization programme managers. However, the position papers may also be of interest to international funding agencies, the vaccine manufacturing industry, the medical community and the scientific media.

Summary and conclusions

Tetanus is an infectious bacterial disease caused by *Clostridium tetani*. Under favourable anaerobic conditions, such as in dirty, necrotic wounds, this ubiquitous bacillus may produce tetanospasmin, an extremely potent neurotoxin. This toxin blocks inhibitory neurotransmitters in the central nervous system and causes the muscular stiffness and spasms typical of generalized tetanus. The disease may affect any age group, and case-fatality rates are high even where modern intensive care is available. The overwhelming majority of tetanus cases are birth-associated and occur in developing countries among newborn babies or in mothers following unclean deliveries and poor post-natal hygiene. Tetanus in children and adults following injuries may also constitute a considerable public health problem.

Protection against tetanus is antibody-dependent and can be achieved only through active (tetanus vaccine) or passive (tetanus-specific immunoglobulin) immunization. Tetanus vaccines are based on tetanus toxoid, a modified neurotoxin that induces protective antitoxin. The immunized mother passes antitoxin via the placenta to her fetus, thereby preventing neonatal tetanus. Tetanus toxoid vaccines are available as single toxoid (TT), combined with diphtheria toxoid (DT) or low-dose diphtheria toxoid (dT) and in combination with diphtheria and pertussis vaccines (DTwP, DTaP, dTaP or dTaP). Vaccines containing DT are used for children aged <7 years and dT-containing vaccines for individuals aged ≥7 years. As a rule, vaccine combinations containing diphtheria toxoid (D or d) and tetanus toxoid, rather than tetanus toxoid alone, should be used when immunization against tetanus is indicated. The DTP combination (primarily for children aged under 1 year) has been part of WHO's Expanded Programme on Immunization since its inception in 1974. Several new combinations containing DTP/DTaP have been marketed, including

Vaccin antitétanique

Notes de synthèse: position de l'OMS concernant les vaccins antitétaniques

Conformément à son mandat qui est de fournir aux Etats Membres des orientations sur les questions de politique de santé, l'OMS publie une série de notes de synthèse régulièrement mises à jour sur les vaccins et les associations vaccinales utilisables contre des maladies ayant une importance pour la santé publique internationale. Ces notes, qui s'intéressent principalement à l'utilisation des vaccins dans les programmes de vaccination à grande échelle, résument les informations générales essentielles relatives aux maladies et vaccins respectifs et concluent par la position actuelle de l'OMS concernant leur utilisation dans le contexte mondial. Ces notes ont été examinées par un certain nombre d'experts au sein et en dehors de l'OMS et, depuis avril 2006, sont revues et approuvées par le Groupe consultatif d'experts des stratégies de vaccination. Elles sont principalement destinées aux responsables nationaux de la santé publique et aux administrateurs de programmes de vaccination. Toutefois, elles peuvent également présenter un intérêt pour les bailleurs de fonds internationaux, les fabricants des vaccins, la communauté médicale et les médias scientifiques.

Résumé et conclusions

Le tétanos est une maladie bactérienne infectieuse provoquée par *Clostridium tetani*. Dans des conditions d'anaérobiose favorables, telles celles présentées par des plaies nécrotiques souillées, ce bacille ubiquitaire peut produire de la tétanospasme, une neurotoxine extrêmement puissante qui bloque les neuromédiateurs inhibiteurs du système nerveux central et provoque la raideur et les spasmes musculaires caractéristiques du tétanos généralisé. Cette maladie peut toucher n'importe quelle classe d'âge, et les taux de létalité sont élevés même lorsqu'on dispose de soins intensifs modernes. La grande majorité des cas de tétanos sont associés à la naissance et surviennent dans les pays en développement chez les nouveau-nés ou chez les mères à la suite d'accouchements et de soins postnatals ayant eu lieu dans de mauvaises conditions d'hygiène. Le tétanos rencontré chez l'enfant et chez l'adulte suite à des lésions traumatiques peut également constituer un problème de santé publique considérable.

La protection contre le tétanos repose sur les anticorps et ne peut être obtenue que par une vaccination active (vaccin antitétanique) ou passive (immunoglobuline spécifique). Les vaccins antitétaniques sont préparés à partir de l'anatoxine tétanique, une neurotoxine modifiée qui induit la production d'une antitoxine protectrice. La mère ainsi vaccinée transmet l'antitoxine par voie placentaire à son fœtus, prévenant ainsi tout risque de tétanos néonatal. Les vaccins préparés à partir d'anatoxine tétanique sont disponibles sous plusieurs formes: anatoxine seule (TT), anatoxine associée avec de l'anatoxine diphtérique (DT) ou avec de l'anatoxine diphtérique faiblement dosée (dT) et en association avec les vaccins antidiphtériques et anti-coquelucheux (DTc, DTcA, dTcA ou dTcA). On utilise les vaccins DT chez les enfants <7 ans et les vaccins dT à partir de 7 ans. En règle générale, les associations vaccinales contenant de l'anatoxine diphtérique (D ou d) et de l'anatoxine tétanique doivent être utilisées de préférence à l'anatoxine tétanique seule lorsqu'une vaccination contre le tétanos est indiquée. Le vaccin associé DTC (dans un premier temps pour les enfants âgés de moins d'1 an) fait partie du programme élargi de vaccination de l'OMS depuis sa création en 1974. Plusieurs nouvelles associations contenant du DTC/DTcA ont

vaccines against hepatitis B, *Haemophilus influenzae* type b and poliomyelitis. Tetanus toxoid is considered very safe, even for use in immunodeficient individuals.

In countries with effective immunization programmes and good standards of hygiene, maternal and neonatal tetanus (MNT) has been largely eliminated (<1 case per 1000 live births at the district level), but tetanus may on rare occasions affect inadequately immunized people, primarily among the elderly. A remarkable reduction in the number of MNT cases has also been achieved in many developing countries. Nonetheless, in 2004, an estimated 40 million pregnant women were still in need of immunization against birth-associated tetanus, and about 27 million children did not complete their primary tetanus immunization series.

The goals of tetanus control are primarily (i) to eliminate MNT globally; and (ii) to achieve and sustain high coverage of 3 doses of DTP and of appropriate booster doses in order to prevent tetanus in all age groups.

A childhood tetanus immunization schedule of 5 doses is recommended. The primary series of 3 doses of DTP3 (DTwP or DTaP) should be given in infancy (age <1 year), with a booster dose of a tetanus toxoid-containing vaccine ideally at age 4–7 years and another booster in adolescence, e.g. at age 12–15 years. The exact timing of the booster doses should be flexible to take account of the most appropriate health service contacts in different countries. Where a high percentage of children, including girls, attend school, school-based immunization programmes should be used where feasible to deliver the booster doses. Special efforts to reach school non-attenders will be needed.

In many countries, non-neonatal tetanus is still a significant public health problem, particularly among children, adolescents and young adults. Tetanus in young individuals commonly reflects poor coverage of the national childhood immunization programme. Obstacles to delivery of the recommended doses of tetanus toxoid-containing vaccines should be identified and forceful measures taken to improve programmatic performance in all districts.

In addition to the childhood vaccination programme, an extra tetanus toxoid-containing dose to adults will provide additional assurance of long-lasting, possibly life-long protection. Therefore, a sixth dose should be recommended for adults, e.g. at the time of the first pregnancy or during military service. Those who receive their first tetanus vaccine doses as adolescents or adults require a total of only 5 appropriately spaced doses to obtain the same long-term protection.

In countries where MNT remains a public health problem, special attention should be given to immunizing women of childbearing age. As a minimum strategy, eligible pregnant women should be routinely immunized at their first contact with antenatal clinics or other

été commercialisées, comprenant le vaccin anti-hépatite B, le vaccin anti-*Haemophilus influenzae* type b et le vaccin antipoliomyélique. L'anatoxine tétanique est considérée comme étant très sûre, même chez des sujets immunodéficients.

Dans les pays disposant de programmes de vaccination efficaces et de bonnes règles d'hygiène, le tétanos maternel et néonatal (TMN) a été en grande partie éliminé (<1 cas pour 1000 naissances vivantes au niveau du district), mais cette maladie peut encore en de rares occasions toucher des gens insuffisamment vaccinés, principalement parmi les personnes âgées. Une réduction remarquable du nombre de cas de TMN a également été obtenue dans de nombreux pays en développement. Néanmoins, en 2004, 40 millions de femmes enceintes étaient encore en attente d'une vaccination contre le tétanos selon les estimations et près de 27 millions d'enfants n'avaient pas achevé leur série d'injections de primo-vaccination antitétanique.

Les objectifs de la lutte antitétanique sont principalement (i) d'éliminer le TMN dans le monde; (ii) d'obtenir et de maintenir une couverture élevée par les 3 doses de DTC et les rappels appropriés de façon à prévenir le tétanos dans toutes les classes d'âge.

On recommande actuellement un calendrier de vaccination antitétanique durant l'enfance de 5 doses. La première série de 3 doses de DTC (DTCe ou DTCa) doit être administrée chez le très jeune nourrisson (âge < 1 an) et être suivie d'une dose de rappel d'un vaccin contenant l'anatoxine tétanique entre l'âge de 4 à 7 ans et d'une autre dose de rappel au cours de l'adolescence, c'est-à-dire entre 12 et 15 ans. Le moment exact auquel on doit injecter les rappels doit être souple afin de tenir compte des contacts avec les services de santé les plus appropriés dans les différents pays. Lorsqu'un pourcentage élevé des enfants, y compris des filles, est scolarisé, on passera lorsque c'est possible par des programmes de vaccination scolaires pour administrer les rappels. Des efforts particuliers pour atteindre les enfants qui ne vont pas à l'école seront nécessaires.

Dans bon nombre de pays, le tétanos non néonatal représente toujours un problème de santé publique important, en particulier chez les enfants, les adolescents et les jeunes adultes. L'apparition d'un tétanos chez des sujets jeunes est souvent le reflet d'une mauvaise couverture du programme national de vaccination infantile. Il convient alors d'identifier les obstacles à la fourniture des doses recommandées de vaccins contenant l'anatoxine tétanique et de prendre des mesures énergiques pour améliorer l'efficacité des programmes dans l'ensemble des districts.

En plus des programmes de vaccination infantile, une dose supplémentaire d'un vaccin contenant l'anatoxine tétanique administrée aux adultes permettra une meilleure assurance de disposer d'une protection de longue durée, voire d'une protection à vie. Une sixième dose est donc recommandée chez l'adulte, à l'occasion par exemple de la première grossesse ou au cours du service militaire. Ceux qui reçoivent leur première dose de vaccin antitétanique à l'adolescence ou à l'âge adulte n'ont besoin en tout que de 5 doses convenablement espacées afin d'obtenir la même protection à long terme.

Dans les pays où le TMN demeure un problème de santé publique, une attention particulière devrait être accordée à la vaccination des femmes en âge de procréer. Au minimum, les femmes enceintes pouvant en bénéficier devraient être systématiquement

health services offering vaccination. Pregnant women with an inadequate or unknown immunization history should always receive 2 doses of tetanus toxoid-containing vaccine: the first dose as early as possible during pregnancy and the second dose at least 4 weeks later. Efforts should be made to complete the recommended series of 5 immunizations, e.g. when the mother brings her baby for vaccinations and in connection with subsequent pregnancies, while respecting the minimum intervals between doses.

In districts with limited access to routine vaccination services and where the elimination target (<1 case per 1000 live births) has not been met, the "high-risk approach" to control MNT should be adopted. This approach targets women of childbearing age by offering 3 doses of tetanus toxoid, usually during a 12-month period. Promotion of improved childhood immunization and clean deliveries is part of this initiative.

The type of tetanus prophylaxis that is required following injuries depends on the nature of the lesion and the history of previous immunizations.¹ Passive immunization using tetanus antitoxin, preferably of human origin, is essential for treatment and occasionally also for prophylaxis (e.g. in cases of dirty wounds in incompletely immunized people). While tetanus antitoxin should be readily available in all countries, its use cannot substitute for the need to achieve and sustain high tetanus vaccination coverage.

Improved national surveillance and reporting systems, including district-level data analysis, are essential for rational planning of immunization efforts, including high-risk approaches against MNT.

Background

Tetanus is a frequently fatal infectious disease caused by toxigenic strains of the bacillus *C. tetani*. The disease remains an important public health problem in many parts of the world, particularly in the poorest districts of tropical developing countries, where tetanus morbidity and mortality are dominated by MNT. In 2002, the total number of deaths caused by tetanus worldwide was estimated at 213 000, of which neonatal tetanus was estimated to represent about 180 000 and maternal tetanus possibly as many as 15 000–30 000 deaths.

Tetanus is readily preventable through immunization and tetanus toxoid-containing vaccines, which are included in childhood immunization programmes all over the world. To obtain long-lasting immunity, however, booster doses are required. Where national immunization programmes have maintained high coverage with TT-containing vaccines for several decades, tetanus has become very rare, but occurs occasionally in the elderly and other non- or insufficiently immunized people. In countries where the national immunization programme has been less success-

ment vaccinées lors de leur premier contact avec le dispensaire prénatal ou d'autres services offrant la vaccination. Les femmes enceintes ayant des antécédents vaccinaux insuffisants ou inconnus doivent toujours recevoir 2 doses de vaccin contenant l'anatoxine tétanique: la première dose dès que possible au cours de la grossesse et la seconde à au moins 4 semaines d'intervalle. On s'efforcera d'administrer la série de 5 vaccinations recommandées, par exemple lorsque la mère amène son enfant pour des vaccinations et à l'occasion de grossesses ultérieures, tout en respectant les intervalles minimum recommandés entre les doses.

Dans les districts où l'accès à des services de vaccination systématique est limité et où la cible de l'élimination (<1 cas pour 1000 naissances vivantes) n'a pas été atteinte, on adoptera l'«approche haut risque» pour lutter contre le TMN. Cette approche cible les femmes en âge de procréer en leur offrant 3 doses d'anatoxine tétanique, en général sur une période de 12 mois. Les efforts en faveur d'une meilleure vaccination au cours de l'enfance et des accouchements « propres » font partie de cette initiative.

Le type de prophylaxie antitétanique nécessaire à la suite d'une blessure dépend de la nature de la lésion et des antécédents vaccinaux.¹ Une vaccination par l'antitoxine tétanique, de préférence d'origine humaine, est indispensable au traitement et parfois également à la prophylaxie (par exemple dans le cas de plaies souillées chez des sujets incomplètement vaccinés). Si le sérum antitétanique doit être facilement disponible dans tous les pays, son utilisation ne saurait se substituer à la nécessité d'obtenir et de maintenir une couverture élevée par la vaccination antitétanique.

Des systèmes nationaux de surveillance et de notification améliorés, comprenant l'analyse des données à l'échelon du district, sont indispensables pour pouvoir planifier de façon rationnelle les efforts de vaccination, y compris dans le cadre des approches «haut risque» contre le TMN.

Généralités

Le tétanos est souvent une maladie infectieuse mortelle provoquée par des souches toxigènes du bacille tétanique. Cette maladie constitue encore un problème de santé publique important dans de nombreuses parties du monde, en particulier dans les districts les plus pauvres des pays en développement tropicaux, où la morbidité et la mortalité tétaniques sont dominées par le TMN. En 2002, on estimait à 213 000 le nombre total de décès provoqués par le tétanos dans le monde, dont 180 000 environ étaient dus au tétanos néonatal et peut-être jusqu'à 15 000–30 000 au tétanos maternel.

Le tétanos est facilement évitable par la vaccination et les vaccins contenant de l'anatoxine tétanique figurent dans les programmes de vaccination infantile du monde entier. Cependant, pour obtenir une immunité de longue durée, des rappels sont nécessaires. Lorsque les programmes nationaux de vaccination ont maintenu pendant plusieurs décennies une couverture élevée par des vaccins contenant de l'anatoxine tétanique, cette maladie devient très rare, mais apparaît occasionnellement chez les personnes âgées et autres sujets non vaccinés ou qui l'ont été insuffisamment. Dans les pays où le programme national de vaccination a été moins efficace,

¹ Summary guide to tetanus prophylaxis in routine wound management. In: Heymann DL, ed. *Control of communicable diseases manual*, 18th ed. Washington, DC, American Public Health Association, 2004:532; *Surgical care at the district hospital*. Geneva, World Health Organization, 2003:4–12.

¹ Summary guide to tetanus prophylaxis in routine wound management. In: Heymann DL, ed. *Control of communicable diseases manual*, 18th ed. Washington, DC, American Public Health Association, 2004:53; *Surgical care at the district hospital*. Genève, Organisation mondiale de la Santé, 2003:4–12.

ful, many women of childbearing age lack protection against birth-associated tetanus.

The pathogen and the disease

C. tetani is a spore-forming, strictly anaerobic bacillus. Spores are prevalent in the environment, particularly in the soil of warm and moist areas, and may be carried in the intestinal tracts of humans and animals. When introduced into necrotic wounds, the spores may convert to toxin-producing tetanus bacilli. The site of entry of *C. tetani* is in some cases unknown or is no longer visible at the time of symptoms. Maternal tetanus is a consequence of unclean delivery or abortion practices, and neonatal tetanus occurs when unclean instruments are used to cut the umbilical cord or when contaminated material is used to cover the umbilical stump in babies without protective concentrations of tetanus-specific antibody.

The most important toxin of *C. tetani* is the highly potent tetanospasmin. This toxin blocks inhibitory neurotransmitters in the central nervous system and causes the muscular stiffness and spasms typical of generalized tetanus.

The incubation period of tetanus usually varies between 3 and 21 days (median 7 days, range 0–>60 days). In most cases, neonatal tetanus starts 3–14 days after birth. In more than 80% of cases, tetanus presents as a generalized spastic disease. Characteristic features are early spasms of the facial muscles (trismus or “lock-jaw” and “risus sardonicus”) followed by spasm of the back muscles (opisthotonos) and sudden, generalized tonic seizures (tetanospasms). Spasm of the glottis may cause sudden death. In neonatal tetanus, generalized spasms are commonly preceded by inability to suck or feed and excessive crying. The overall tetanus case-fatality rate varies between 10% and 70%, depending on treatment, age and general health of the patient. Without hospitalization and intensive care, fatality is almost 100% among the oldest and the youngest patients. In settings with optimal care, it may be reduced to 10–20%.

The diagnosis is based on clinical features and not on laboratory confirmation. The WHO definition of neonatal tetanus is an illness occurring in a child who has the normal ability to suck and cry in the first 2 days of life but who loses this ability between days 3 and 28 of life and becomes rigid and has spasms.

Treatment includes wound care, where required, as well as management of the symptoms and complications associated with the disease. Prompt treatment with antitetanus immunoglobulins and appropriate antibiotics may prevent further progression of the disease but is unlikely to influence existing pathology.

Protective immune response

Immunity to tetanus is antibody-mediated and depends upon the ability of antitoxins to neutralize tetanospasmin. Recovery from clinical tetanus does not result in protection against the disease in the future; immunity can be obtained by active or passive immunization only. Maternal tetanus antitoxin passes via the placenta to the fetus. Hence, when pregnant women receive a booster dose or the second dose

de nombreuses femmes en âge de procréer ne sont pas protégées contre le risque de tétanos au moment de l'accouchement.

Le germe et la maladie

C. tetani est un bacille strictement anaérobie qui produit des spores. Celles-ci sont abondantes dans l'environnement, en particulier dans les sols chauds et humides et peuvent être transportées dans l'intestin de l'homme et des animaux. Lorsqu'elles sont introduites dans des plaies nécrotiques, ces spores peuvent se transformer en bacilles tétaniques producteurs de toxine. Dans certains cas on ignore quelle est la porte d'entrée de *C. tetani* ou bien elle n'est plus visible lorsque les symptômes apparaissent. Le tétanos maternel est une conséquence des accouchements pratiqués dans de mauvaises conditions d'hygiène ou de certaines pratiques d'avortement et le tétanos néonatal apparaît chez l'enfant lorsque des instruments souillés sont utilisés pour couper le cordon ombilical ou lorsque l'on utilise des produits contaminés pour recouvrir le moignon ombilical chez des enfants dépourvus de concentrations protectrices d'anticorps antitétaniques.

La toxine la plus importante de *C. tetani* est la très puissante tétaospasmine. Cette toxine bloque les neuromédiateurs inhibiteurs du système nerveux central et provoque la raideur et les spasmes musculaires caractéristiques du tétanos généralisé.

La période d'incubation du tétanos est en général de 3 à 21 jours (médiane 7 jours, intervalle 0–>60 jours). Dans la plupart des cas, le tétanos néonatal apparaît dans les 3 à 14 jours suivant la naissance. Dans plus de 80% des cas, la maladie se présente sous une forme spastique généralisée. Ses traits caractéristiques sont des spasmes précoces des muscles de la face (trismus ou «spasme cynique»), suivis de spasmes des muscles du dos (opisthotonos) et de convulsions toniques soudaines généralisées (tétaospasmes). Un spasme de la glotte peut provoquer brutalement le décès. Dans le tétanos néonatal, les spasmes généralisés sont couramment précédés par une incapacité à téter ou à s'alimenter et par des pleurs excessifs. Le taux de létalité général du tétanos se situe entre 10% et 70%, en fonction du traitement, de l'âge et de l'état général des malades. Sans hospitalisation ni soins intensifs, il est de près de 100% chez les malades les plus âgés et les plus jeunes. Avec des soins optimaux, il peut être réduit à 10–20%.

Le diagnostic est basé sur les caractéristiques cliniques et non sur une confirmation au laboratoire. La définition OMS du tétanos néonatal est la suivante: une maladie survenant chez un enfant qui tète et pleure normalement au cours des 2 premiers jours de la vie, mais qui perd cette capacité entre le troisième et le 28^e jour et présente des raideurs et des spasmes.

Le traitement comprend les soins apportés à la plaie le cas échéant, ainsi que la prise en charge des symptômes et complications associés à la maladie. Un traitement rapide par des immunoglobulines antitétaniques et des antibiotiques appropriés peut permettre d'éviter que la maladie ne progresse davantage mais a peu de chances de modifier la pathologie existante.

Réponse immunitaire protectrice

L'immunité contre le tétanos met en jeu les anticorps et dépend de la capacité des antitoxines à neutraliser la tétaospasmine. La guérison d'un tétanos clinique n'entraîne pas une protection contre la maladie pour l'avenir; l'immunité ne peut être obtenue que par une vaccination active ou passive. L'anatoxine tétanique maternelle est transmise au fœtus par le placenta. Ainsi, lorsque les femmes enceintes reçoivent un rappel ou la seconde dose d'une

of a primary series at least 2 weeks before delivery, both mother and child are protected against birth-associated tetanus. If this last dose is given within 2 weeks of delivery, the time for a booster response to occur may be insufficient to guarantee protection of the newborn. Nonetheless, the opportunity should still be taken to give the dose that is due in order to provide protection during future pregnancies.

The minimum amount of circulating antitoxin that, in most cases, ensures immunity to tetanus is assay-specific. With in vivo neutralization tests or modified ELISA assays, concentrations exceeding 0.01 IU/ml are usually considered protective, whereas antitoxin concentrations of at least 0.1–0.2 IU/ml are defined as positive when standard ELISA techniques are used for this assessment. Cases of tetanus have been documented, however, in people with antitoxin concentrations above these thresholds. Hence, a “protective antibody concentration” may not be considered a guarantee of immunity under all circumstances. The aim should be to sustain high antibody concentrations throughout life.

Tetanus toxoid

Tetanus vaccines are based on tetanus toxoid. Conventional production includes growth of toxigenic strains of *C. tetani* in a liquid medium that favours toxin production, toxin harvest by filtration, detoxification by formaldehyde and several steps of purification and sterilization. To increase immunogenicity, the toxoid is adsorbed to aluminium or calcium salts. Administration of adsorbed tetanus toxoid is by intramuscular injection. Tetanus toxoid is stable and can withstand exposure to temperatures of around 20 °C for months and storage at 37 °C for a few weeks without significant loss of potency. However, the vaccine is destroyed in 2 hours at 56 °C. Tetanus toxoid-containing vaccines should be stored at +4 (2–8) °C; vaccines that have been frozen should not be used.

Toxoid potency is expressed in international units (IU) of protection and is determined by assessing the survival of immunized guinea-pigs or mice following challenge with tetanus toxin. According to WHO requirements,² the potency of monovalent tetanus toxoid shall be no less than 40 IU (determined in guinea-pigs or in mice) per dose (0.5 ml), and at least 40 IU (determined in guinea-pigs) or 60 IU (determined in mice) per dose when tetanus toxoid is used in combination with diphtheria and whole-cell pertussis vaccines.

On the international market, tetanus toxoid is available as a single antigen vaccine (TT), in combination with diphtheria toxoid (DT or dT, depending on the quantity of diphtheria toxoid) and in combination with diphtheria toxoid and pertussis vaccine (DTwP, DTaP, dTaP or dTap). The pertussis vaccine is specified as whole-cell (wP) or acellular (aP) and as aP or ap, depending on the quantity of pertussis antigens. Furthermore, DTwP- or DTaP-containing combi-

série de primovaccination au moins 2 semaines avant l'accouchement, la mère et l'enfant sont protégés contre le tétanos lors de l'accouchement. Si cette dernière dose est administrée dans les 2 semaines précédant l'accouchement, la durée nécessaire pour qu'une réponse immunologique se produise peut être insuffisante pour garantir la protection du nouveau-né. Néanmoins, on saisira tout de même l'occasion d'administrer la dose nécessaire de façon à assurer la protection pour les grossesses futures.

La quantité minimum d'antitoxine circulante qui, dans la plupart des cas, garantit une immunité contre le tétanos, dépend des dosages. Dans les tests de neutralisation in vitro ou les tests ELISA modifiés, on estime que les concentrations dépassant 0,01 UI/ml sont habituellement protectrices, tandis que des concentrations d'antitoxine d'au moins 0,1–0,2 UI/ml sont considérées comme positives lorsqu'on applique des techniques ELISA standards pour cette évaluation. Toutefois, des cas de tétanos ont été documentés chez des gens ayant des concentrations d'antitoxine supérieures à ces seuils. Une «concentration d'anticorps protectrice» ne peut donc être considérée comme une garantie d'immunité dans toutes les situations. Le but doit être de maintenir des concentrations d'anticorps élevées pendant toute la vie.

Anatoxine tétanique

Les vaccins antitétaniques sont préparés à partir d'anatoxine tétanique. La production habituelle suppose la croissance de souches de toxigènes *C. tetani* dans un milieu liquide favorisant la production de toxine, la récolte de cette toxine par filtration, sa detoxification par le formaldéhyde et plusieurs étapes de purification et de stérilisation. Pour accroître son immunogénicité, l'anatoxine est absorbée sur des sels d'aluminium ou de calcium. L'administration de cette anatoxine tétanique adsorbée se fait par injection intramusculaire. L'anatoxine tétanique est stable et peut supporter une exposition à des températures avoisinant les 20°C pendant plusieurs mois et une conservation à 37°C pendant quelques semaines, sans perdre beaucoup de son activité. Toutefois, le vaccin est détruit en 2 heures à 56°C. Les vaccins contenant de l'anatoxine tétanique doivent être conservés à +4 (2–8) °C; les vaccins qui ont été congelés ne doivent pas être employés.

L'activité de l'anatoxine est exprimée en unités internationales (UI) de protection et est déterminée en évaluant la survie de cobayes et de souris vaccinés après inoculation d'épreuve par de la toxine tétanique. Conformément aux normes OMS,² l'activité de l'anatoxine tétanique monovalente ne doit pas être inférieure à 40 UI (déterminée chez le cobaye ou la souris) par dose (0,5 ml), et d'au moins 40 UI (déterminée chez le cobaye) ou 60 UI (déterminée chez la souris) par dose lorsque l'anatoxine tétanique est utilisée en association avec les vaccins antidiphtériques et anticoquelucheux à germes entiers.

Sur le marché international, l'anatoxine tétanique est disponible sous forme de vaccin mono-antigénique (TT), en association avec l'anatoxine diphtérique (DT ou dT, en fonction de la quantité d'anatoxine diphtérique) et en association avec l'anatoxine diphtérique et le vaccin anticoquelucheux (sous forme de DTcE, DTcA, dTcA ou dTcA). Le vaccin anticoquelucheux est à germes entiers (Ce) ou acellulaire (Ca) et sous la forme Ca ou ca, en fonction de la quantité d'antigènes coquelucheux présents. En outre, des associations

² Requirements for diphtheria, tetanus, pertussis and combined vaccines. WHO Technical Report Series, No. 800, 1990, Annex 2; Recommendations for diphtheria, tetanus, pertussis and combined vaccines (Amendments 2003). WHO Technical Report Series, No. 927, 2005, Annex 5.

² Normes relatives au vaccin antidiphtérique, au vaccin antitétanique, au vaccin anticoquelucheux et aux vaccins associés. OMS, Série de Rapports techniques, N° 800, 1990, annexe 2; Recommendations for diphtheria, tetanus, pertussis and combined vaccines (Amendments 2003). OMS, Série de Rapports techniques, N° 927, 2005, annexe 5.

nations have been marketed that include vaccines such as inactivated poliovirus vaccine, hepatitis B and *H. influenzae* type b.

Vaccine efficacy and effectiveness

Whereas protection is incomplete after the first vaccine dose, protective concentrations of antitoxin are achieved in the majority of vaccinees after completion of 2 doses; a third dose induces immunity in almost 100% of those immunized. The interval between the tetanus toxoid-containing doses should be at least 4 weeks. Longer intervals may increase the magnitude and duration of the immune response, but should not be a reason to delay immunization.

Both the efficacy and the effectiveness of tetanus toxoid are well documented. In most clinical trials, efficacy has ranged from 80% to 100%. The introduction of tetanus vaccination in the United States during the 1940s resulted in a decline in the overall incidence of tetanus from 0.4 per 100 000 population in 1947 to 0.02 per 100 000 population at the end of the 1990s. In a double-blind, controlled study in rural Colombia, neonatal tetanus did not occur among infants born to mothers who had received 2 or 3 doses of the vaccine, whereas among unvaccinated controls the mortality rate was 78 per 1000 live births. A similarly significant reduction of neonatal tetanus mortality following the introduction of large-scale tetanus vaccination has been observed in numerous other countries.

Occasionally, failures to provide protection against neonatal tetanus despite previous immunization of the mothers have been reported. In some of these cases, the lack of protection could be explained by inaccurate immunization histories, inappropriate vaccine schedules, use of low-potency vaccines, poor maternal immune response or inadequate placental transfer of antibodies. In malaria-infected pregnant women, the response to tetanus vaccination is similar to that of non-pregnant healthy adults. Data on the effect of malaria on transplacental transfer of tetanus-specific antibodies are inconsistent, but any potential effect is likely to be minor at most. As with other vaccines, the antibody response to tetanus toxoid is impaired in children with AIDS. However, in perinatally HIV-infected children, satisfactory antibody responses were obtained during their first 2 years of life. In HIV-infected adults, the antibody response to tetanus toxoid is less than that in non-infected individuals, but the concentration of antibody is substantial and represents a positive response to immunization.

Duration of protection

The antibody concentration and avidity and also the duration of protection depend on a number of factors, including the age of the vaccinees and the number of and intervals between vaccine doses. Three DTP doses in infancy will give 3–5 years' protection, a further dose or booster (e.g. in early childhood) will provide protection into adolescence, and 1 or 2 more booster(s) will induce immunity well through adulthood – a duration of 20–30 years has been suggested. Booster responses can still be elicited after

contenant du DTcE – ou du DTcA – ont été commercialisées qui comprennent des vaccins comme le VPI, le vaccin anti-hépatite B et le vaccin anti-*H. influenzae* type b.

Efficacité des vaccins

Si la protection est incomplète après la première dose de vaccin, des concentrations protectrices d'anatoxine sont obtenues chez la majorité des gens après la deuxième dose; une troisième dose induit l'immunité chez presque 100% des vaccinés. L'intervalle entre les doses doit être d'au moins 4 semaines. Des intervalles plus longs peuvent accroître l'ampleur et la durée de la réponse immunitaire, mais ne doivent pas être une raison pour retarder la vaccination.

L'efficacité de l'anatoxine tétanique est bien documentée. Dans la plupart des essais cliniques, elle se situe entre 80 et 100%. L'introduction de la vaccination antitétanique aux Etats-Unis au cours des années 1940 a entraîné un déclin de l'incidence générale du tétanos, qui est passée de 0,4 pour 100 000 habitants en 1947 à 0,02 pour 100 000 habitants à la fin des années 90. Dans une étude contrôlée en double aveugle effectuée dans une zone rurale de 2 ou 3 doses de vaccin, alors que chez les témoins non vaccinés le taux de mortalité par tétanos néonatal a été de 78 pour 1000 naissances vivantes. Une réduction tout aussi importante de la mortalité par tétanos néonatal suite à l'introduction de la vaccination antitétanique à grande échelle a été observée dans de nombreux autres pays.

On a signalé dans quelques cas une impossibilité à fournir une protection contre le tétanos néonatal malgré la vaccination préalable des mères. Dans certains d'entre eux, l'absence de protection pourrait s'expliquer par des antécédents vaccinaux erronés, des calendriers vaccinaux inappropriés, l'utilisation de vaccins ayant une faible activité, la mauvaise réponse immunitaire maternelle ou une transmission insuffisante des anticorps par voie placentaire. Chez les femmes enceintes présentant une infestation palustre, la réponse à la vaccination antitétanique est analogue à celle des adultes en bonne santé non gravides. Les données relatives à l'effet de l'infestation palustre sur la transmission transplacentaire des anticorps antitétaniques sont contradictoires, mais il est probable qu'un éventuel effet potentiel soit tout au plus mineur. Comme pour les autres vaccins, la réponse en anticorps à l'anatoxine tétanique est altérée chez les enfants atteints d'un SIDA. Toutefois, chez ceux infectés par le VIH durant la période périnatale, des réponses en anticorps satisfaisantes ont été obtenues au cours des 2 premières années de la vie. Chez les adultes infectés par le VIH, la réponse en anticorps est moins importante que chez les sujets non infectés, mais la concentration d'anticorps est importante et représente une réponse positive à la vaccination.

Durée de la protection

La concentration et l'avidité des anticorps ainsi que la durée de la protection dépendent d'un certain nombre de facteurs, notamment de l'âge des vaccinés, du nombre de doses reçues et de l'intervalle entre ces doses. Trois doses de DTc au cours de la petite enfance conféreront une protection pendant 3 à 5 ans, une dose supplémentaire/rappel (par exemple au début de l'enfance) protégera pendant l'adolescence et 1 ou 2 rappels supplémentaires induiront une immunité pendant une bonne partie de l'âge adulte – 20 à 30 ans ont été suggérés. Des réponses immunitaires peuvent encore être

intervals of 25–30 years, demonstrating the persistence of immunological memory.

Adverse events

Tetanus toxoid used alone or in various fixed combinations is considered very safe. Both TT and dT can be used at any time during pregnancy; immunodeficiency including HIV infection is not a contraindication to their use. Tetanus toxoid causes minor local reactions such as pain and erythema in about 25–85% of cases, occasionally nodules and, very rarely, sterile abscesses (1–10 per million doses administered). Mild systemic reactions including fever, aches and malaise occur in 0.5–1% of vaccinees following booster injections. In general, both local and systemic reactions increase with increasing numbers of doses. Severe generalized adverse events such as anaphylactic reactions and brachial neuritis are extremely rare, 1–6 and 5–10 per million administered doses, respectively. Despite occasional rumours to the contrary, tetanus toxoid-containing vaccines do not contain substances that would have any contraceptive or abortive effect.

General WHO position on vaccines

Vaccines for large-scale public health interventions should meet the current WHO quality requirements;³ be safe and have a significant impact against the actual disease in all target populations; if intended for infants or young children, be easily adapted to the schedules and timing of national childhood immunization programmes; not interfere significantly with the immune response to other vaccines given simultaneously; be formulated to meet common technical limitations, e.g. in terms of refrigeration and storage capacity; and be appropriately priced for different markets.

WHO position on tetanus vaccine

Tetanus toxoid complies well with all the aforementioned general WHO requirements. It is readily available throughout the world both as single antigen and in vaccine combinations.

The goals of tetanus control are primarily (i) to eliminate MNT globally; and (ii) to achieve and sustain high coverage of DTP3 and of appropriate boosters in order to prevent tetanus in all age groups.

Prevention of MNT

Since WHO in 1989 called for global elimination of MNT, the estimated number of neonatal tetanus deaths was reduced from 800 000 worldwide in the 1980s to 180 000 in 2002. Despite impressive progress, neither the original goal of eliminating neonatal tetanus by 1995 nor the subsequent goal of eliminating MNT as a public health problem by 2005 were achieved.

Unfortunately, opportunities to vaccinate pregnant women visiting antenatal clinics or other health centres offering

déclenchées au bout de 25 à 30 ans, montrant ainsi la persistance d'une mémoire immunologique.

Manifestations indésirables

L'anatoxine tétanique utilisée seule ou en associations fixes variées est considérée comme très sûre. La TT ou la dT peuvent être utilisées à n'importe quel moment pendant la grossesse; l'immunodéficience, y compris l'infection à VIH, n'est pas une contre-indication à son utilisation. L'anatoxine tétanique provoque des réactions locales mineures de douleur et d'érythème dans 25 à 85 % des cas, parfois des nodules et très rarement des abcès stériles (1-10 par million de doses administrées). Des réactions générales bénignes à type de fièvre, de douleur et de malaise se produisent chez 0,5 à 1% des vaccinés après les injections de rappel. En général, les réactions locales et générales augmentent avec le nombre de doses reçues. Des manifestations indésirables générales graves telles que des réactions anaphylactiques, et des névrites brachiales sont extrêmement rares, de l'ordre de 1-6 et de 5 à 10 par million de doses administrées, respectivement. En dépit de rumeurs occasionnelles indiquant le contraire, les vaccins contenant l'anatoxine tétanique ne contiennent pas de substances qui auraient un quelconque effet contraceptif ou abortif.

Position générale de l'OMS concernant les vaccins

Les vaccins destinés à des interventions de santé publique à grande échelle doivent satisfaire aux normes et qualités de l'OMS en vigueur;³ doivent être sûrs et avoir un effet important contre la maladie dans toutes les populations cibles; s'ils sont destinés aux nourrissons ou aux jeunes enfants, ils doivent pouvoir être facilement adaptables aux calendriers des programmes nationaux de vaccination infantile; ils ne doivent pas interférer de manière significative avec la réponse immunitaire à d'autres vaccins administrés simultanément; ils doivent être formulés de manière à satisfaire aux contraintes techniques communes, par exemple en ce qui concerne la réfrigération et la capacité de stockage; et leur prix doit être fixé de manière appropriée pour les différents marchés.

Position de l'OMS concernant le vaccin antitétanique

L'anatoxine tétanique satisfait à toutes les normes générales de l'OMS susmentionnées. Elle est facilement disponible partout dans le monde sous forme monoantigénique ou dans des associations vaccinales.

Les objectifs de la lutte antitétanique sont avant tout i) d'éliminer le TMN dans le monde; et ii) d'obtenir et de maintenir une forte couverture du DTC3 et des rappels appropriés de façon à prévenir le tétanos dans toutes les classes d'âge.

Prévention du TMN

Depuis qu'en 1989 l'OMS a lancé un appel en faveur de l'élimination mondiale du TMN, le nombre estimé de décès par tétanos néonatal est passé de 800 000 dans les années 80 à 180 000 en 2002. Malgré des progrès impressionnants, ni l'objectif original d'élimination du tétanos néonatal avant 1995, ni l'objectif ultérieur d'élimination du TMN en tant que problème de santé publique avant 2005, n'ont été atteints.

Malheureusement, les occasions de vacciner les femmes enceintes se rendant dans les dispensaires prénatals ou autres centres de

³ *GPV policy statement*. Geneva, World Health Organization, 1996 (WHO/VSQ/GEN/96.02 Rev.1; available at <http://www.who.int/vaccines-documents/DocsPDF/www9637.pdf>).

³ *Déclaration de politique générale. Déclaration sur la qualité des vaccins*. Genève, Organisation mondiale de la Santé, 1997. Document WHO/VSQ/GEN/96.02 Rev. 1; disponible sur <http://www.who.int/vaccines-documents/DocsPDF/www9643.pdf>

immunization are frequently missed. Furthermore, many pregnant women report to the clinic too late to be protected by tetanus toxoid immunization and do not receive a postpartum dose that would help protect them in later pregnancies.

The “high-risk approach” to control neonatal tetanus should be part of the neonatal tetanus elimination strategy in countries where the elimination target (<1 case per 1000 live births at district level)⁴ has not yet been reached. This approach targets all women of childbearing age and consists of campaign-style immunization (supplementary immunization activities, or SIAs) with 3 doses of TT (or dT) with an interval of at least 4 weeks between doses 1 and 2, and of at least 6 months between doses 2 and 3. Promotion of clean deliveries is part of this approach. In addition to the 3 doses provided in the SIAs, 2 further boosters are needed to provide long-term protection to women with no documented receipt of tetanus toxoid-containing vaccines in childhood. Between 1999 and 2005, approximately 64 million women worldwide received at least 2 doses of tetanus toxoid through this strategy.

Prevention of tetanus in the general population

Although in many developing countries emphasis will remain on the elimination of MNT, simultaneous strengthening of national childhood immunization programmes is required to protect against tetanus occurring in other segments of the population and to provide immunity to future generations of childbearing women. In 2004, about 27 million children worldwide still did not receive the third dose of DTP. Obstacles to optimal delivery of tetanus toxoid-containing vaccines must be identified and forceful measures taken to improve suboptimal immunization programmes.

Most countries with developed or transitional economies have eliminated MNT through a combination of clean deliveries and long-term use of tetanus toxoid-containing vaccines. In these countries, tetanus still occasionally occurs, particularly in elderly individuals who have not received the necessary immunizations. The aims of the tetanus vaccination policy in these settings are to maintain the high coverage of primary immunizations and to ensure protection throughout life with adequate booster doses.

Prevention of tetanus in the case of injury

Although adequately immunized people should have sufficient protection against tetanus, treating physicians may give a dose of tetanus toxoid-containing vaccine in the case of an injury, in addition to other preventive measures. Depending on the severity of the injury and on the reliability of the history of previous tetanus vaccinations, the vaccine should be given if the last dose was administered more than 10 years ago (or 5 years in the case of severe injuries).¹ The immunization schedule should be completed as soon as possible for those who have not received all doses of the basic schedule.

⁴ *Field manual for neonatal tetanus elimination*. Geneva, World Health Organization, 1999 (WHO/N&B/99.14).

santé offrant la vaccination sont fréquemment manquées. De plus, de nombreuses femmes enceintes se rendent au dispensaire trop tard pour être protégées par une vaccination antitétanique et ne reçoivent pas durant le postpartum la dose d'anatoxine qui permettrait de les protéger lors des grossesses suivantes.

La «stratégie du haut risque» pour lutter contre le tétanos néonatal doit faire partie de la stratégie d'élimination du tétanos néonatal dans les pays où la cible d'élimination (<1 cas pour 1000 naissances vivantes au niveau du district)⁴ n'a pas encore été atteinte. Cette stratégie cible l'ensemble des femmes en âge de procréer et consiste en une vaccination sur le mode de la campagne (activités de vaccination supplémentaires) par 3 doses de TT (ou de dT) avec un intervalle d'au moins 4 semaines entre la 1^{re} et la 2^e dose et d'au moins 6 mois entre la 2^e et la 3^e dose. L'action en faveur des accouchements «propres» fait partie de cette stratégie. En plus des 3 doses administrées à l'occasion des activités de vaccination supplémentaires, 2 autres doses sont nécessaires pour conférer une protection à long terme aux femmes pour lesquelles on n'a aucune trace écrite d'une vaccination par l'anatoxine tétanique au cours de l'enfance. Entre 1999 et 2005, près de 64 millions de femmes dans le monde ont reçu au moins 2 doses d'anatoxine tétanique grâce à cette stratégie.

Prévention du tétanos dans la population générale

Même si dans de nombreux pays en développement on va continuer à mettre l'accent sur l'élimination du TMN, le renforcement simultané des programmes nationaux de vaccination infantile est nécessaire pour protéger contre les cas de tétanos survenant dans d'autres segments de la population et immuniser les générations futures de femmes en âge de procréer. En 2004, près de 27 millions d'enfants dans le monde n'avaient toujours pas reçu la troisième dose de DTC. Il convient d'identifier les obstacles à l'administration optimale des vaccins contenant l'anatoxine tétanique et de prendre des mesures énergiques pour améliorer les programmes de vaccination ne fonctionnant pas de façon optimale.

La plupart des pays dont les économies sont développées ou en transition ont éliminé le TMN en associant les accouchements effectués dans de bonnes conditions d'hygiène et l'utilisation à long terme des vaccins contenant l'anatoxine tétanique. Dans ces pays, des cas de tétanos apparaissent encore parfois, en particulier chez les sujets âgés n'ayant pas reçu les doses de vaccin nécessaires. Le but de la politique de vaccination antitétanique dans ces situations est de maintenir une couverture élevée de la primovaccination et d'assurer une protection tout au long de la vie grâce à des rappels suffisants.

Prévention du tétanos en cas de lésion traumatique

Même si les gens correctement vaccinés sont censés être suffisamment protégés contre le tétanos, les médecins traitants peuvent administrer une dose d'un vaccin contenant l'anatoxine tétanique en cas de lésion traumatique, en plus des autres mesures préventives. En fonction de la gravité de la lésion et de la fiabilité des antécédents vaccinaux de la personne, le vaccin doit être administré si la dernière dose injectée remonte à plus de 10 ans (ou 5 ans dans le cas de lésions graves).¹ Le calendrier vaccinal doit être mené à son terme dans les meilleurs délais pour ceux qui n'ont pas reçu toutes les doses du calendrier de base.

⁴ *Manuel d'application pratique pour l'élimination du tétanos néonatal*. Genève, Organisation mondiale de la Santé, 1999 (WHO/N&B/99.14); disponible sur <http://www.who.int/vaccines-documents/DOCSPDF99/www99.25.pdf>

In addition, passive immunization using tetanus antitoxin, preferably of human origin, may be needed for prophylaxis (e.g. in cases of dirty wounds in incompletely immunized individuals). Such antitoxin is also essential in the treatment of tetanus cases and should be readily available in all countries.

Tetanus vaccination schedules

The choice of primary schedule as well as of the number and timing of boosters varies considerably among countries, often reflecting national epidemiological, programmatic and economic considerations. Ideally, all individuals should receive a total of 5 doses of tetanus toxoid-containing vaccine in childhood, followed by a sixth dose in early adulthood to provide added assurance of protection throughout the childbearing years, and possibly for life. Even after many years, an interrupted primary- or booster-dose schedule should not be restarted; the schedule is simply continued with the next dose that is due. All doses received over an individual's lifetime should be recorded on their lifelong vaccination card.

DTwP or DTaP combinations should be used for children aged <7 years, whereas for older age groups dT combinations should be used in order to also promote and sustain diphtheria immunity. In some countries, one or more formulation(s) of dTap, which has reduced the content of both pertussis and diphtheria antigens, are now available for adolescents and adults. WHO recommends that the primary series of 3 doses should be given in infancy (aged <1 year). Where pertussis is of particular risk to young infants, DTP immunization should be started at age 6 weeks and 2 subsequent doses should be given at intervals of at least 4 weeks (e.g. at weeks 10 and 14).

The exact timing of the booster doses should be flexible to take account of the most appropriate health service contacts in different countries. Ideally, a booster dose should be offered at age 4–7 years followed by another booster in adolescence, e.g. at age 12–15 years. In addition to the childhood vaccination programme, an extra dose to adults will further assure long-lasting, possibly lifelong protection. A sixth dose is therefore recommended for adults, for example at the time of the first pregnancy or during military service.

With an increasing percentage of children worldwide, including girls, attending school, school-based immunization programmes will become increasingly important and should be implemented where feasible. Female enrolment rates in various grades should be considered when deciding which age groups should be offered immunization against tetanus at school. A school-based immunization approach may be linked to other important health services, including health education. In the future, new vaccines, e.g. the vaccine against human papillomavirus, could also benefit from a school-based delivery system, but efforts to reach school non-attenders will be important for all these interventions.

For previously non-immunized adolescents and adults, the recommended schedule is 2 doses administered at least 4 weeks apart followed by a third dose administered at

En outre, la vaccination passive au moyen de sérum antitétanique, de préférence d'origine humaine, peut être nécessaire pour la prophylaxie (par exemple, en cas de plaies souillées chez les sujets incomplètement vaccinés). Ce sérum antitétanique est également indispensable pour traiter les cas de tétanos et doit être facilement disponible dans tous les pays.

Calendriers de vaccination antitétanique

Le choix du calendrier de primovaccination ainsi que le nombre et le moment où sont administrés les rappels varie considérablement d'un pays à l'autre et est souvent le reflet des considérations nationales d'ordre épidémiologique, programmatique et économique. L'idéal serait que tous les individus reçoivent au total 5 doses d'un vaccin contenant l'anatoxine tétanique au cours de l'enfance, suivies d'une sixième dose au début de l'âge adulte afin d'assurer une protection supplémentaire aux femmes en âge de procréer, voire une protection à vie. Même après de nombreuses années, un calendrier de primovaccination ou de rappels interrompu ne doit pas être recommencé; il sera simplement poursuivi par l'administration de la dose suivante nécessaire. Toutes les doses reçues par un individu au cours de sa vie doivent être enregistrées sur sa carte de vaccination.

Les vaccins associés DTcE ou DTcA doivent être utilisés chez l'enfant de moins de 7 ans, tandis que pour les classes d'âge supérieur, on utilisera des associations dT pour également renforcer et maintenir une immunité antidiphtérique. Dans certains pays, une ou plusieurs formulations de dTcA, qui ont une teneur réduite en antigènes coquelucheux et diphtériques, sont désormais disponibles pour les adolescents et les adultes. L'OMS recommande que la première série de 3 doses soit administrée durant la petite enfance (avant 1 an). Lorsque la coqueluche constitue un risque particulier pour les jeunes nourrissons, on démarrera la vaccination DTc à l'âge de 6 semaines et les 2 doses suivantes seront espacées d'au moins 4 semaines (c'est-à-dire administrées à 10 et 14 semaines).

La programmation de l'administration exacte des rappels doit être souple afin de tenir compte des contacts avec les services de santé les plus appropriés selon le pays. L'idéal serait qu'on offre un rappel entre 4 et 7 ans, suivi d'un autre pendant l'adolescence, par exemple entre 12 et 15 ans. En plus du programme de vaccination infantile, une dose supplémentaire administrée aux adultes garantira une protection à long terme et peut-être à vie. Une sixième dose est par conséquent recommandée chez l'adulte, par exemple au moment de la première grossesse ou au cours du service militaire.

Etant donné le pourcentage accru d'enfants, y compris des filles, qui sont scolarisés dans le monde, les programmes de vaccination en milieu scolaire vont prendre de plus en plus d'importance et devront être mis en oeuvre lorsque c'est possible. Les taux de recrutement des filles dans des différentes classes devront être pris en compte lorsqu'on décidera des classes d'âge auxquelles offrir la vaccination contre le tétanos à l'école. La stratégie de vaccination en milieu scolaire pourrait être liée à d'autres services de santé importants, notamment à l'éducation pour la santé. A l'avenir, de nouveaux vaccins, par exemple le vaccin contre le papillomavirus humain, pourraient également bénéficier d'un système d'administration en milieu scolaire, mais pour toutes ces interventions, il sera important de s'efforcer d'atteindre les enfants qui ne vont pas à l'école.

Concernant les adolescents et les adultes qui n'ont jamais été vaccinés, le calendrier recommandé est de 2 doses espacées d'au moins 4 semaines, suivies d'une troisième dose administrée au moins

Summary table **Immunizations with diphtheria–tetanus–pertussis (DTP) and diphtheria toxoid (Td) vaccines required to obtain long-term protection^a against tetanus**

Tableau récapitulatif **Vaccinations par le vaccin antidiphtérique-antitétanique-anticoquelucheux (DTC) et par les anatoxines tétaniques et diphtériques (Td) nécessaires pour obtenir une protection à long terme contre le tétanos^a**

Recommended schedule – Calendrier recommandé	DTP – DTC	DTP – DTC	DTP – DTC	dT	dT	dT
	Before age one or as early as possible after age 6 weeks, with ≥4 weeks intervals – Avant un an ou dès que possible après l'âge de 6 semaines; doses espacées d'au moins 4 semaines			e.g. 4–7 years – entre 4 et 7 ans	e.g. 12–15 years – entre 12 et 15 ans	Early adulthood – au début de l'âge adulte
Adolescents and adults with no previous immunization – Adolescents et adultes n'ayant jamais été vaccinés	dT	dT	dT	dT	dT	
	As early as possible – Dès que possible	At least 4 weeks later – Au minimum 4 semaines plus tard	At least 6 months later – Au minimum 6 mois plus tard	At least 1 year later – Au minimum 1 an plus tard	At least 1 year later – Au minimum 1 an plus tard	
Pregnant women with no previous immunization (or unreliable immunization information) – Femmes enceintes n'ayant jamais été vaccinées (ou dont la vaccination est douteuse)	dT	dT	dT	dT	dT	
	As early as possible in first pregnancy – Dès que possible au cours de la première grossesse	At least 4 weeks later – Au moins 4 semaines plus tard	At least 6 months later, or in next pregnancy – Au moins 6 mois plus tard ou au cours de la grossesse suivante	At least 1 year later, or in next pregnancy – Au moins 1 an plus tard ou au cours de la grossesse suivante	At least 1 year later, or in next pregnancy – Au moins 1 an plus tard ou au cours de la grossesse suivante	
Pregnant women with 3 childhood DTP doses – Femmes enceintes ayant reçu 3 doses de DTC durant l'enfance	dT	dT	dT			
	As early as possible in first pregnancy – Dès que possible au cours de la première grossesse	At least 4 weeks later – Au moins 4 semaines plus tard	At least 1 year later – Au moins 1 an plus tard			
Pregnant women with 4 childhood DTP doses – Femmes enceintes ayant reçu 4 doses de DTC pendant l'enfance	dT	dT				
	As early as possible in first pregnancy – Dès que possible au cours de la 1 ^{re} grossesse	At least 1 year later – Au moins 1 an plus tard				
Supplementary immunization activities in high-risk areas (women of childbearing age) – Activités de vaccination supplémentaires dans les zones à haut risque (femmes en âge de procréer)	dT	dT	dT	dT	dT	
	During round 1 – Au cours de la 1 ^{re} tournée	During round 2, at least 4 weeks after round 1 – Au cours de la 2 ^e tournée, au moins 4 semaines après	During round 3, at least 6 months after round 2 – Au cours de la 3 ^e tournée, au moins 6 mois après	At least 1 year later, (e.g. in next pregnancy) – Au moins 1 an plus tard (grossesse suivante)	At least 1 year later, or in next pregnancy – Au moins 1 an plus tard ou au cours de la grossesse suivante	

^a Other tetanus-containing combination vaccines can be used as per national immunization schedules. – D'autres vaccins associés contenant le vaccin antitétanique peuvent être utilisés suivant les calendriers nationaux de vaccination.

least 6 months after the second, and subsequent boosters at least 1 year apart. Those who receive their first tetanus vaccine doses as adolescents or adults require a total of only 5 appropriately spaced doses to obtain long-term protection.

In countries where MNT remains a public health problem, pregnant women for whom reliable information on previous tetanus vaccinations is not available should receive at least 2 doses of tetanus toxoid-containing vaccine

6 mois après la seconde, les rappels ultérieurs étant administrés à au moins 1 an d'écart. Les personnes qui reçoivent leur première dose de vaccin antitétanique à l'adolescence ou à l'âge adulte ont seulement besoin de 5 doses correctement espacées pour obtenir une protection à long terme.

Dans les pays où le TMN demeure un problème de santé publique, les femmes enceintes pour lesquelles on ne dispose pas de renseignements fiables concernant d'éventuelles vaccinations antitétaniques antérieures doivent recevoir au moins 2 doses de vaccins

(normally dT) with an interval of at least 4 weeks between the doses. To ensure protection for a minimum of 5 years, a third dose should be given at least 6 months later. A fourth and fifth dose should be given at intervals of at least 1 year, e.g. during subsequent pregnancies, in order to ensure long-term protection. Pregnant women who have received only 3 doses of DTP in early infancy should receive 2 doses of a tetanus toxoid-containing vaccine with a minimal interval of 4 weeks. Those who received 4 doses of tetanus vaccine during their childhood need only 1 booster dose, which should be given at the first opportunity. In both scenarios, to provide protection throughout childbearing age, a sixth dose would be needed after at least 1 year.

Improved national surveillance and reporting systems, including district-level data analysis, are essential for rational planning of immunization efforts, including high-risk approaches against MNT. ■

contenant l'anatoxine tétanique (normalement dT) espacées d'au moins 4 semaines. Pour conférer une protection de minimum 5 ans, une troisième dose doit être administrée 6 mois plus tard au moins. Une quatrième et une cinquième doses devront être administrées à au moins 1 an d'écart, par exemple au cours des grossesses suivantes, pour assurer une protection à long terme. Les femmes enceintes qui n'ont reçu que 3 doses de DTC au cours de la petite enfance doivent recevoir 2 doses d'un vaccin contenant de l'anatoxine tétanique espacées d'au moins 4 semaines. Celles qui ont reçu 4 doses de vaccin antitétanique au cours de l'enfance n'ont besoin que d'un rappel, qui doit être administré à la première occasion. Dans ces deux scénarios, pour conférer une protection pendant toute la période où les femmes sont en mesure de procréer, une sixième dose serait nécessaire au bout d'au moins 1 an.

Des systèmes nationaux améliorés de surveillance et de notification, comprenant l'analyse des données à l'échelon du district, sont indispensables pour pouvoir planifier rationnellement les efforts de vaccination, notamment les «stratégies du haut risque» contre le TMN. ■

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- (1) WHO WWW SERVER: Use WWW navigation software to connect to the WER pages at the following address: <http://www.who.int/wer/>
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2016 MIDTERM REVIEW OF THE GLOBAL VACCINE ACTION PLAN

STRATEGIC
ADVISORY
GROUP OF
EXPERTS ON
IMMUNIZATION

I EXECUTIVE SUMMARY

At the midpoint of the Global Vaccine Action Plan, or GVAP (2012-2020), the Strategic Advisory Group of Experts on Immunization (SAGE) remains gravely concerned that progress toward the goals to eradicate polio, eliminate measles and rubella, eliminate maternal and neonatal tetanus, and increase equitable access to lifesaving vaccines is too slow. Despite improvements in individual countries and a strong global rate of new vaccine introduction, global average immunization coverage has increased by only 1% since 2010.

In 2015, 68 countries fell short of the target to achieve at least 90% national coverage with the third dose of diphtheria-tetanus-pertussis vaccine. Not only that, 26 countries reported no change in coverage levels and 25 countries reported a net decrease in coverage since 2010. The 16 countries that have made measurable progress since 2010 are to be commended for reaching more people, especially vulnerable and marginalized members of society with immunization. Some of the countries with the highest numbers of unvaccinated people have made the most progress, including the Democratic Republic of the Congo, Ethiopia and India, and even though coverage targets have not been achieved in these countries, they are moving forward in the right direction.

The 111 countries that entered the decade with high immunization coverage and sustained it through 2015 are already setting their sights on more aggressive goals, additional vaccines, and more equitable coverage. Immunization programmes in these countries can lead the way by increasing access to other public health interventions and providing a platform for the delivery of preventive health services throughout the life course. Vaccine research and development is progressing rapidly, and an expanding pipeline of new vaccines underscores the need to build health systems that can reliably reach new target age groups.

The members of the SAGE are steadfast and passionate believers in the power of immunization to give individuals and their families a better start in life and to protect people from a growing array of debilitating illnesses. Immunization is one of the world's most effective and cost-effective tools against the threat of emerging diseases and has a powerful impact on social and economic development. Recognizing the role that immunization plays in ensuring good health and the role that good health plays in achieving sustainable development, the SAGE has supported the inclusion of immunization indicators to measure progress toward the Sustainable Development Goals.

The next four years present unprecedented opportunities for countries to leverage the attention and support that immunization receives and apply it for the benefit of people everywhere. Strident efforts on the part of all countries and immunization stakeholders are required to catch up and achieve GVAP goals by 2020.

The SAGE has made 9 recommendations which are detailed at the end of this report:

1. Demonstrate stronger leadership and governance of national immunization systems
2. Prioritize immunization system strengthening
3. Secure necessary investments to sustain immunization during polio and Gavi transitions
4. Improve surveillance capacity and data quality and use
5. Enhance accountability mechanisms to monitor implementation of Global and Regional Vaccine Action Plans
6. Achieve elimination targets for maternal and neonatal tetanus, measles and congenital rubella syndrome
7. Resolve barriers to timely supply of affordable vaccines in humanitarian crisis situations
8. Support vaccine R&D capacity in low- and middle-income countries
9. Accelerate the development and introduction of new vaccines and technologies

TABLE OF CONTENTS

1.	PROGRESS ON INDICATORS	6
2.	SAGE VIEWPOINT	10
3.	AREAS OF STRENGTH	12
4.	AREAS OF VULNERABILITY	14
5.	THREATS TO FUTURE PROGRESS	16
6.	CAUSE FOR HOPE	18
7.	WHY IMMUNIZATION MATTERS NOW MORE THAN EVER	19
8.	SAGE RECOMMENDATIONS	20
ANNEX 1: STRATEGIC ADVISORY GROUP OF EXPERTS ON IMMUNIZATION (SAGE) DECADE OF VACCINES WORKING GROUP MEMBERSHIP		23

1. PROGRESS ON INDICATORS

Now at the midpoint of GVAP implementation, the SAGE notes that while some progress has been made in individual countries, midpoint targets were missed for polio eradication, neonatal tetanus elimination, measles and rubella elimination and routine immunization coverage. The current pace of progress must change if GVAP goals are to be achieved by 2020.

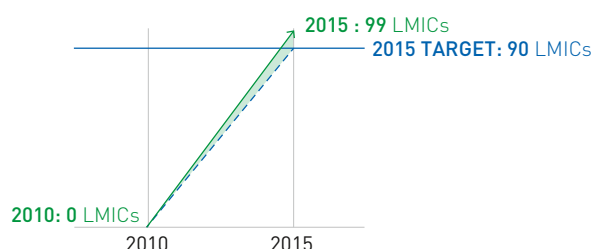
The current pace of global progress must change if GVAP goals are to be achieved by 2020

GVAP TARGETS FOR 2015 WERE MISSED
IN ALL BUT ONE CATEGORY

EXCEEDED

VACCINE INTRODUCTION:

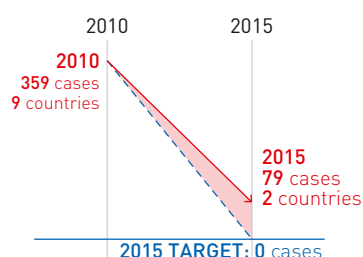
Number of low or middle income countries to have introduced one or more new or under-utilized vaccine since 2010



MISSED

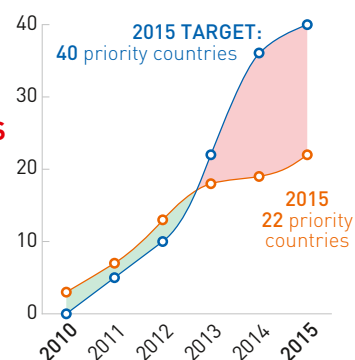
POLIO:

Number of new cases of paralytic poliomyelitis due to wild poliovirus



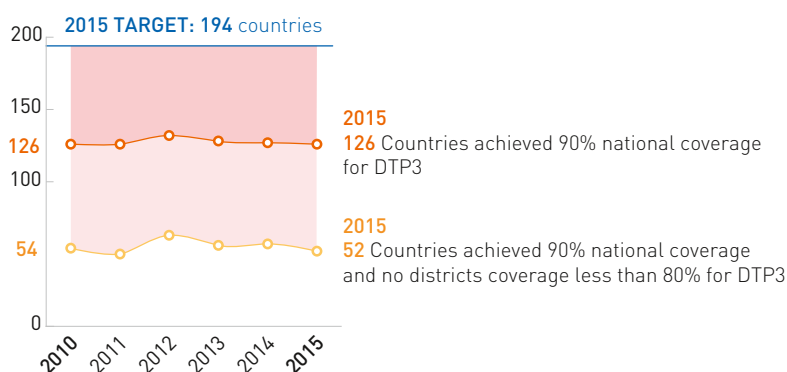
MATERNAL AND NEONATAL TETANUS ELIMINATION:

Number of countries verified for elimination



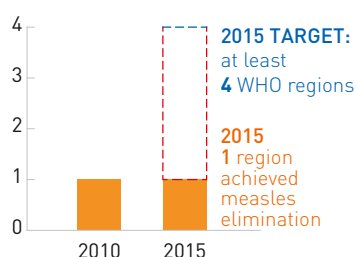
COVERAGE AND EQUITY:

Number of countries with national vaccination coverage of 90%, with no district's coverage less than 80%



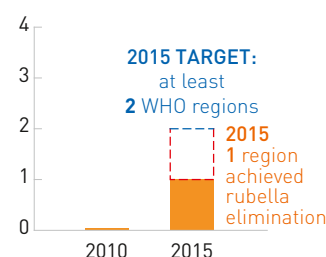
MEASLES:

Number of WHO regions to achieve measles elimination



RUBELLA:

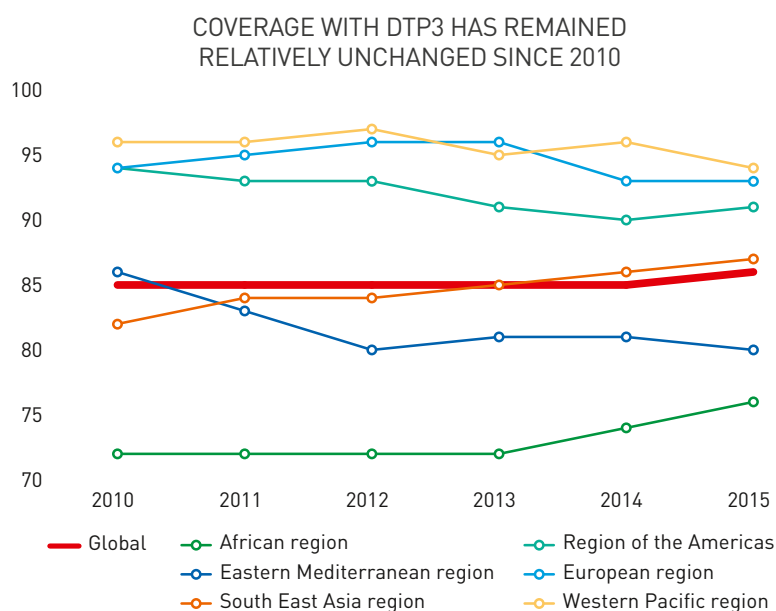
Number of WHO regions verified for rubella and CRS elimination



Source: Joint Reporting Forms, 2010 – 2015

IMMUNIZATION COVERAGE AND EQUITY TARGETS

Since 2010, there has been only a marginal overall improvement in the indicator measuring vaccine coverage and equity.¹ While 126 Member States (65%) achieved at least 90% coverage with DTP3 in 2015, most had already achieved this goal before the decade began. Only 15 additional countries have achieved this level of coverage since 2010. Further, a scant 52 Member States (27%) out of 88 with valid district-level data have achieved equity targets of national level coverage of $\geq 90\%$ and coverage of $\geq 80\%$ in every district.



The overall change in global average coverage with DTP3 was 1% between 2010 and 2015

Source: WHO and UNICEF Estimates for National Immunization Coverage (WUENIC), 2010 – 2015

Among the 68² countries that have not yet achieved national-level coverage of 90% or higher, 16 (8%) have made progress, while 25 countries (13%) report a net decrease in coverage since 2010. Another 26 countries (13%) have seen no net change in DTP3 coverage since 2010. Only one country that started the decade with coverage above 80% reported a net increase in coverage by 2015, underscoring just how difficult it is to increase coverage above 80%. The overall change in global average coverage with DTP3 was 1% (from 85% to 86%) between 2010 and 2015.

Among the countries that are showing progress, India, Ethiopia and the Democratic Republic of the Congo stand out because they are all counted among the twenty countries with the largest numbers of unvaccinated people, and their efforts to increase coverage are making a difference in closing the immunization gap. These efforts need to expand to reduce the socio-economic and geographic inequities that still persist in each of these countries.

Countries with stagnant or decreasing coverage tell a different story. A small subset of countries is struggling to provide reliable immunization services in the face of political instability and emergency situations. Syria, Yemen, and South Sudan are counted among them. The majority of countries with coverage below 90% are failing to meet targets despite relatively stable and predictable environments. Here, factors such as weak health infrastructure, less than optimal governance, and lack of integration leading to missed opportunities for immunization play larger roles.

¹ This indicator counts the number of countries achieving 90% national coverage with the third dose of diphtheria-tetanus-pertussis containing vaccine (DTP3), with all districts achieving coverage greater than or equal to 80%.

² South Sudan joined WHO in 2012, therefore is not included in 2010–2015 trends analysis.

DISEASE CONTROL TARGETS

There are three indicators measuring progress toward disease elimination and eradication goals. All three targets were missed in 2015. A disappointing setback in polio eradication was the emergence of several cases of wild poliovirus in Nigeria in 2016, after more than 24 months with no reported cases across the whole African continent. This virus has circulated undetected since 2011 in an area of the country with very limited access to health services, signaling a worrisome chink in the armor for polio surveillance. Progress was made in maternal and neonatal tetanus elimination (MNTE), with 22 countries validated for MNTE since 2010 but 18 countries have yet to achieve this goal. While such progress is positive, it is sluggish; it is the third time a global target has been set and missed for maternal and neonatal tetanus elimination.

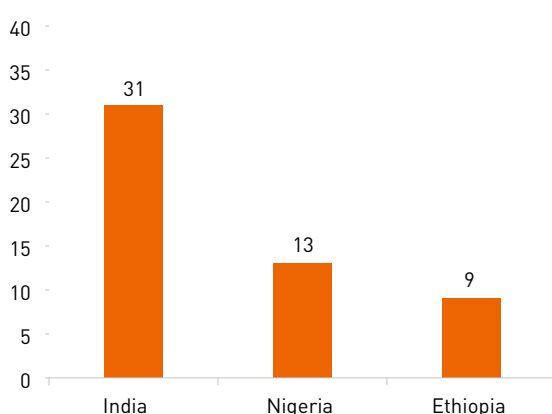
It is the third time a global target has been set and missed for maternal and neonatal tetanus elimination

Measles and rubella elimination is also progressing slower than expected. Since 2010, global measles incidence has decreased by 21% from 50 cases per million to 39.3 in 2015, which is substantially higher than the global 2015 target of fewer than five cases per million population. Measles outbreaks have occurred in numerous countries – a result of sub-optimal immunization coverage through both routine services and campaigns, along with increased susceptibility in older age groups. While outbreaks are being reported, the quality of the outbreak data do not always provide the comprehensive information required to take corrective actions. Surveillance for measles remains weak in many countries with low reporting sensitivity, limiting the ability of country managers to use data for programmatic and strategic decision-making. Rubella control lags even further behind, as 45 Member States still have not yet introduced the vaccine and two regions (African and Eastern Mediterranean) have not yet set rubella elimination or control targets. One region (the Americas) successfully eliminated the endemic transmission of rubella and congenital rubella syndrome and was verified in 2015.

45 Member States have not yet introduced rubella vaccine

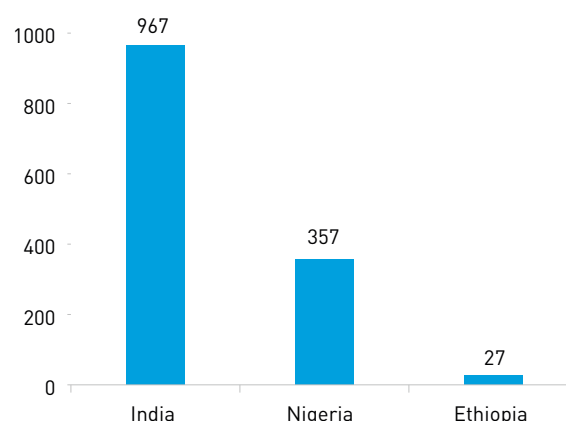
THE POTENTIAL IMPACT OF REDUCED POLIO RESOURCES IN THE THREE COUNTRIES WITH THE HIGHEST MEASLES BURDEN IS DRAMATIC

Contribution (%) to global measles mortality



Source: WHO, Department of Evidence, Information and Research estimates for child causes of death, 2000-2015 (updated 5 February 2016).

Current number of full-time-equivalent polio-funded staff working on measles and rubella in the countries with the highest measles mortality*



Source: Boston Consulting Group study in Afghanistan, Angola, Chad, DR Congo, Ethiopia, India, Nigeria, Pakistan, Somalia, South Sudan for the Global Polio Eradication Initiative, 2015

* The current full-time-equivalent number is calculated using the % of time dedicated to measles and rubella by the total number of polio-funded staff.

NEW VACCINE INTRODUCTION

Since 2010, 99 low- and middle-income countries (73%) have introduced at least one new and under-utilized vaccine (excluding IPV) to their national immunization programme and sustained vaccine use for at least 12 months, making a total of 160 vaccine introductions. Gavi, the Vaccine Alliance has provided support to 64 of these countries. Of the 99 countries that have introduced at least one vaccine, 47 have introduced and sustained more than one vaccine, including 14 upper-middle income countries, 19 lower-middle income countries and 14 low-income countries.

160 vaccine introductions have been made in 99 countries since 2010

RESEARCH AND DEVELOPMENT

Every two years, the SAGE reviews progress against research and development (R&D) goals. These goals include the licensure and launch of a vaccine against one or more major currently non-vaccine preventable diseases and the licensure and launch of at least one platform delivery technology.

In July 2015, the first malaria vaccine to be assessed by a regulatory agency received a positive opinion from the European Medicines Agency (EMA). This step is a pre-requisite for a WHO policy recommendation and licensure for the use of the vaccine in national immunization programmes. A vaccine against dengue has been licensed in multiple countries and at least two other candidate dengue vaccines are in Phase III trials, with several other candidates in earlier clinical development. In November 2016, enrollment will begin for a Phase III clinical trial of an HIV vaccine in South African adults.

TB vaccines have proven extremely difficult to develop, as there is no correlate of protection to guide vaccine design. However, innovative trial designs, new animal models, a new Human Model Consortium and incorporation of novel immunologic approaches and technologies, such as micro-array patches, have breathed new life into TB vaccine R&D and expanded the pipeline.

A new blueprint guiding R&D responses to emergencies has allowed Zika vaccine development to progress at unprecedented speed

Candidate vaccines against other priority diseases, including universal influenza vaccine and vaccines for maternal immunization, such as respiratory syncytial virus (RSV), group B strep, tetanus toxoid and pertussis are moving through preclinical and clinical development.

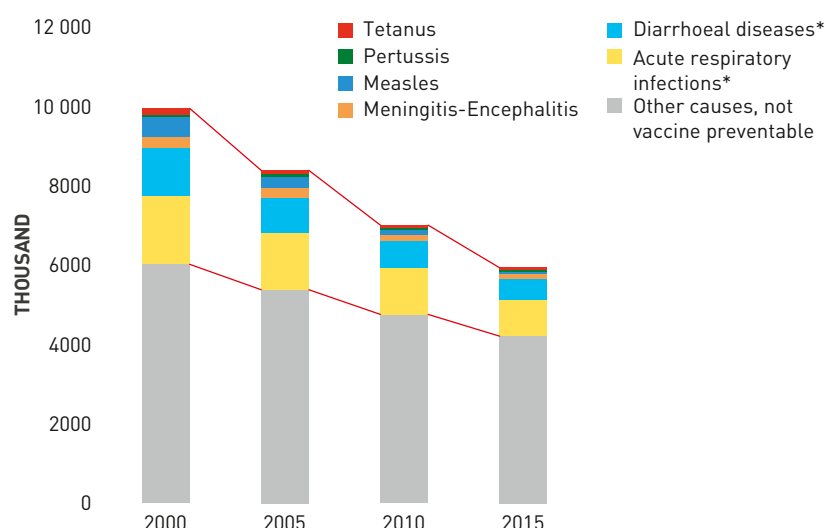
In response to the threat of new emerging pathogens, WHO has developed a blueprint to guide an R&D response to emergencies. The section on vaccines was informed by lessons learnt during the development of Ebola vaccine. Applying this blueprint to Zika vaccine development has allowed R&D to progress at an unprecedented speed.

2. SAGE VIEWPOINT

A bright spot at the midpoint of the GVAP is the rate of new vaccine introduction in low- and middle income countries and the impact this suggests for under-five morbidity and mortality. While modeling studies are not available to quantify the vaccine-attributable decrease in mortality in children under five, the step decline in pneumonia and diarrhoea morbidity and mortality that was measured in a few countries following the introduction of pneumococcal and rotavirus vaccines, respectively, suggests a significant contribution. As long as new vaccine introduction can be expanded further in more countries that continue to have high rates of deaths due to pneumonia and diarrhoea, high and equitable coverage with these vaccines remains a winning strategy for public health impact.

High and equitable coverage with new vaccines remains a winning strategy for public health impact

VACCINES HAVE BEEN KEY CONTRIBUTORS TO THE GLOBAL REDUCTION IN UNDER-FIVE MORTALITY SINCE 2000



Source: WHO, Department of Evidence, Information and Research estimates for child causes of death, 2000-2015 (updated 5 February 2016).

*Note: The reduction in mortality for vaccine-preventable diseases counts the impact of other interventions. Not all diarrhoeal diseases or acute respiratory infections are vaccine-preventable.

The SAGE is also pleased to note the substantial progress made in vaccine R&D, particularly toward HIV, malaria, dengue, and tuberculosis vaccines.

The rapid progress made in vaccine R&D since 2010 underscores the urgent need to expand clinical trial capacity in low- and middle-income countries, strengthen the ability of NRAs to evaluate and license vaccines and technologies, and begin implementation research for vaccines and platform delivery technologies much earlier in the process.

Progress in vaccine R&D underscores the urgent need to expand clinical trial capacity, strengthen NRAs, and begin implementation research earlier

MAJOR CONCERNS

The good news regarding new and future vaccines, however is shadowed by the unhurried global progress toward achieving other GVAP targets. There are still 19 million un-vaccinated and under-vaccinated children in the world, representing the least privileged members of society: those who are fleeing disaster, marginalized, dispossessed or simply uncounted. Each day that such populations are excluded from the benefits of immunization represents a lost opportunity to build stronger and healthier communities.

Repeatedly missing targets for eradication and elimination goals results in prolonged and more expensive campaigns that ultimately threaten global enthusiasm for such endeavors and undermine community demand for immunization services. Insufficient funding for disease control initiatives, particularly in non-Gavi countries, has stymied efforts to introduce rubella-containing vaccine, conduct high-quality measles campaigns among older age groups, and commit to or achieve national and regional elimination goals. The poor quality of campaigns in many countries has not sufficiently limited the circulation of infectious diseases, resulting in outbreaks that must be managed using resources that might be better spent on routine immunization services.

Ultimately, an immunization programme that cannot deliver services to the majority of the population is a signal of a weak health system, one that is less resilient in the face of emergency situations and the very real threat of global introductions of emerging pathogens like Ebola, Yellow Fever and Zika viruses.

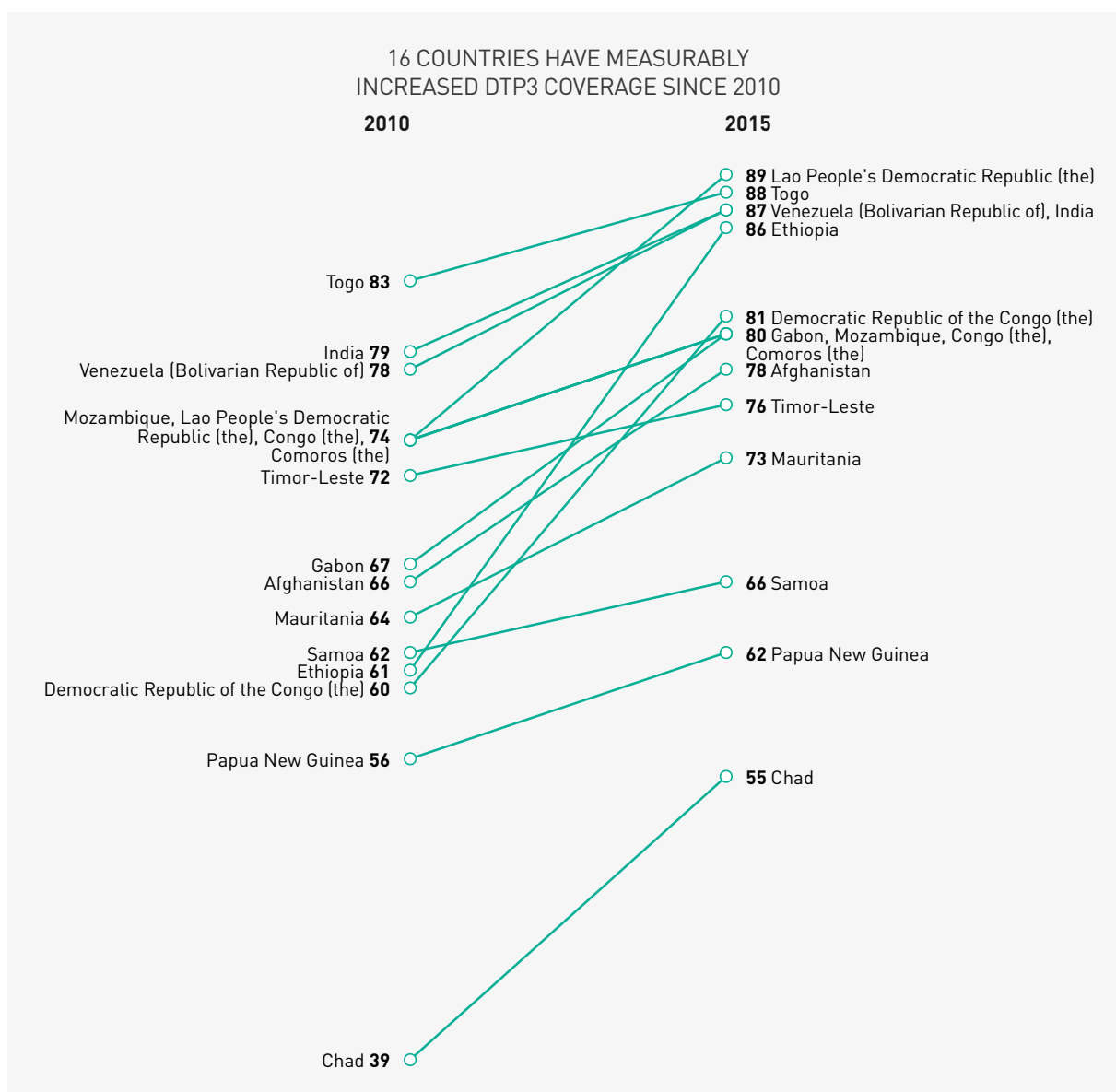
At the midpoint of the GVAP, the SAGE is concerned that more countries haven't embraced the opportunity to strengthen immunization programmes and harness the global energy and enthusiasm that seems to be growing for vaccines. Countries must make more concerted efforts to strive for and reach GVAP goals by 2020, and those countries that have achieved or made forward progress toward achieving GVAP goals must work to sustain those efforts over time.

The current pace of global progress toward achieving GVAP targets is too slow

Weak immunization programmes are less resilient in the face of emergencies and less able to manage and recover from the introduction of emerging pathogens

3. AREAS OF STRENGTH

A deeper look the countries that improved immunization coverage since 2010 confirms what is already known about what it takes to change immunization programme performance for the better.



Source: WHO and UNICEF Estimates for National Immunization Coverage (WUENIC), 2010-2015

Leadership. There are several outstanding examples of how courageous and committed leadership can change immunization performance for the better. More than 116 Member States have formed independent National Immunization Technical Advisory Groups (NITAGs) to guide decision-making on vaccine introductions, immunization schedules and immunization policies. Uganda and Nepal are among the first countries in their regions to enact immunization laws to mandate vaccination and establish a mechanism whereby donors, individuals and private sector entities can contribute to a national immunization fund. Elected leaders in the Democratic Republic of the Congo have formed a Parliamentary Network to secure funds and monitor disbursements and activities that have been promised by the government. For the moment, Uganda has not seen progress in national coverage since 2010, however coverage

in Nepal increased from 82% to 91% and coverage in the Democratic Republic of the Congo has increased from 60% to 81% since 2010.

Investment in health systems. Leadership has also been demonstrated in the form of meaningful investments in health systems and health workforces. Ethiopia recently built 16,000 new health centers, purchased 2,000 battery-free solar refrigerators for facilities lacking access to electricity, trained a new cadre of paid health extension workers and established a health development “army” of three million volunteers to facilitate access to immunization throughout the country. Since 2010 when these investments were first made, immunization coverage in Ethiopia has soared from 61% to 86%. Similarly, India has made new investments in health systems, replacing and repairing cold chain equipment, training thousands of Accredited Social Health Activist workers, and using microplanning to support immunization. This and an intensification of services through campaigns resulted in DTP3 coverage jumping from 79% to 87%, meaning two million more children received the vaccine in 2015 than in 2010. The SAGE will be watching with interest to see if this progress can be sustained over time.

Dedicated people. The day-to-day work of providing reliable immunization services can be difficult in low-resource environments. Immunization and technical staff face countless frustrations and bottlenecks that they doggedly overcome in a sometimes thankless environment of high pressure and expectations. Too often, health workers are not sufficiently paid or wait months for payment, and the weight of the immunization programme is carried on their shoulders. We commend the civil society organizations, agency staff, volunteers and particularly community-based health workers who risk their lives in fragile states and conflict areas in places like Syria, Yemen and South Sudan to provide immunization services to communities living in those areas. It is thanks to these people that, for example, no less than 41% of the population was immunized in Syria in 2015.

Known interventions. With three decades of experience to draw from, immunization staff at all levels have developed an arsenal of tools and strategies for achieving high performance in almost any environment. Applying the Reaching Every Community strategy in 22 districts in Chad, for example, has paid off, contributing to hard-won coverage gains from 39% to 55%. Progress in Nigeria is notable as well, particularly given the size and complexity of the country. Government and partner support for the immunization programme has grown, and the response to recent polio cases has been swift. A lot of effort has been put toward improving primary health care in recent years resulting in coverage gains from 49% to 56% since 2014. More of this effort is needed to bridge the divide between current and desired coverage, but the trend is in the right direction.

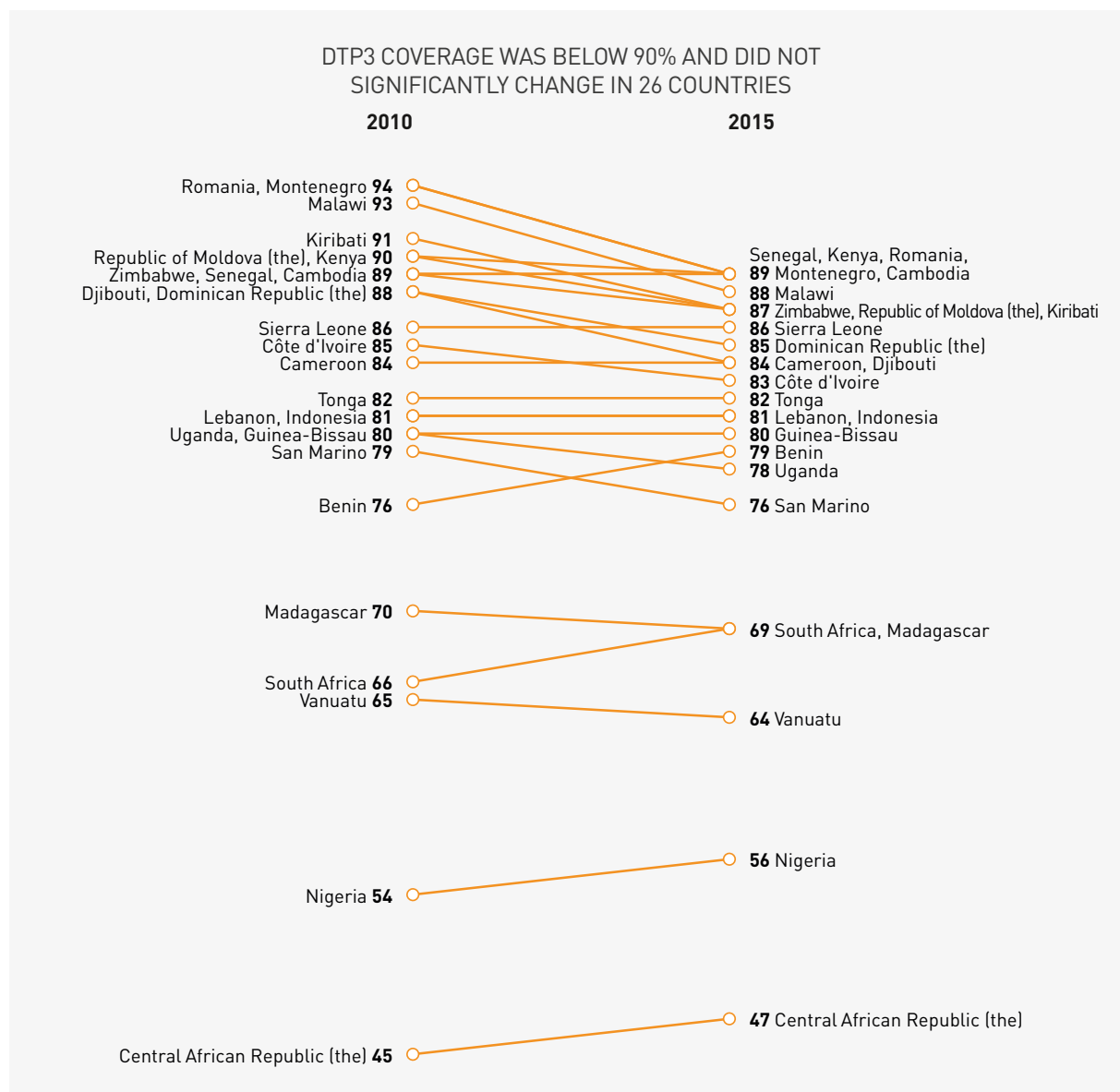
Accountability. Global, regional, and national commitments to immunization, plans, budgets and activities are only hollow promises when no one is accountable for their completion. At the global level, the GVAP has been a positive mechanism to hold WHO Member States, UN agencies, and other global immunization partners to their word and take notice when progress is off track. The recent Ministerial Conference for Immunization in Africa, attended by Ministers of Health from 70 Member States in the African and East Mediterranean regions, is a good example of leveraging Regional Vaccine Action Plans to hold Ministers of Health to account for overseeing progress along an agreed set of indicators. Country-level accountability mechanisms have been harnessed in several countries, using Civil Society Organizations, legal frameworks and National Immunization Technical Advisory Groups (NITAGs) to oversee the implementation of immunization plans and track progress toward agreed targets.

Health system investments in Ethiopia have contributed to coverage improvements from 61% in 2010 to 86% in 2015

We commend the civil society organizations, agency staff, volunteers, and particularly community-based health workers who risk their lives in fragile states and conflict areas to provide immunization

4. AREAS OF VULNERABILITY

Although each country is unique, there are several common factors that inhibit progress and limit the quality and outcomes of immunization programmes.



Source: WHO and UNICEF Estimates for National Immunization Coverage (WUENIC), 2010-2015

Low commitment. The most common and corrosive force found within countries with stagnant or declining coverage is a general lack of interest and commitment to immunization at all levels. In countries with low commitment or apathetic leadership, immunization programmes suffer from lack of sufficient and/or reliable funds, inadequate human resource capacity and low motivation to address chronic bottlenecks that hinder performance. While vaccine affordability remains a legitimate concern for a subset of countries, it does not always excuse a lack of domestic investment in immunization programmes. Domestic investment in immunization services must increase even further, especially in countries transitioning from Gavi support. This investment is worthwhile and provides ample return in the form of lower long-term healthcare costs and higher proportions of the population able to contribute to

Domestic investment in immunization services must increase even further, especially in countries transitioning from Gavi support

community vitality and economic viability. Improving coverage with the vaccines currently in the schedule is the most economically sound strategy available to countries to ensure that when newer, more expensive vaccines are introduced, they have a powerful impact on health and the economy.

Inaccessibility and weak surveillance. Physical or political inaccessibility is another factor obstacle facing immunization programmes. Whether a community is inaccessible because of a lack of trust, lack of roads or lack of supplies, unimmunized pockets of the population should give countries cause for concern. Surveillance is especially important in these areas, as diseases can circulate and spread to other areas. The recent polio resurgence in Nigeria is a sobering example of the consequences that can arise when populations are out of reach of both immunization and surveillance systems.

Poor governance. Poor government oversight has resulted in very costly declines in immunization performance in several countries. In a handful of countries, procurement issues have resulted in persistent stockouts, such that families no longer seek or expect immunization services from their local health posts. Not surprisingly, these issues demotivate health staff and take a toll on the quality of services. Some countries with decentralized health systems have experienced five or more years of prolonged confusion over roles and responsibilities within the immunization programme, with inadequate accountability mechanisms and oversight from national and district levels. When this happens, district level funding for immunization can vary widely with almost no transparency into how resources are prioritized, making it impossible to orchestrate immunization improvements across districts.

Outdated data culture. The SAGE has raised the issue of poor quality data each year since writing GVAP assessment reports. The lack of reliable data and the failure to use data make decisions at all levels of government is pervasive and troubling. Few countries have a method of collecting immunization data from the private sector. Similarly, few countries have the ability to analyze data to locate unimmunized pockets. Even coverage data can vary widely between administrative reports and surveys, making it very difficult to know how well or poorly programmes are doing, and what to prioritize next. After improving the accuracy of immunization data collected in Mexico, for example, the country reported coverage levels almost 10 percentage points lower than previous years. The SAGE commends the Mexican government for this work because it has succeeded in making under- and unimmunized populations visible to the health system. As countries reach higher levels of coverage, their data will need to become more granular and specific. District level coverage is now requested in WHO-UNICEF Joint Reporting Forms, but the availability and quality of that data remains deficient.

Disconnect. There is a persistent disconnect between immunization and the broader health system agenda. Immunization stakeholders are underrepresented in Universal Health Care discussions, leaving immunization priorities overlooked and opportunities lost to leverage immunization for the benefit of other health programmes. Disconnect also exists between global, regional and country bodies, making it difficult to communicate needs and coalesce on desired outcomes. Despite a recommendation for Regional Committees to oversee implementation of Regional Vaccine Action Plans, it appears that very few Regional Committees are tracking progress and holding countries to account. At the country level, a surprising lack of awareness of the GVAP persists in many places. Areas of disconnect represent major missed opportunities for better collaboration and synergies both within immunization and across health disciplines.

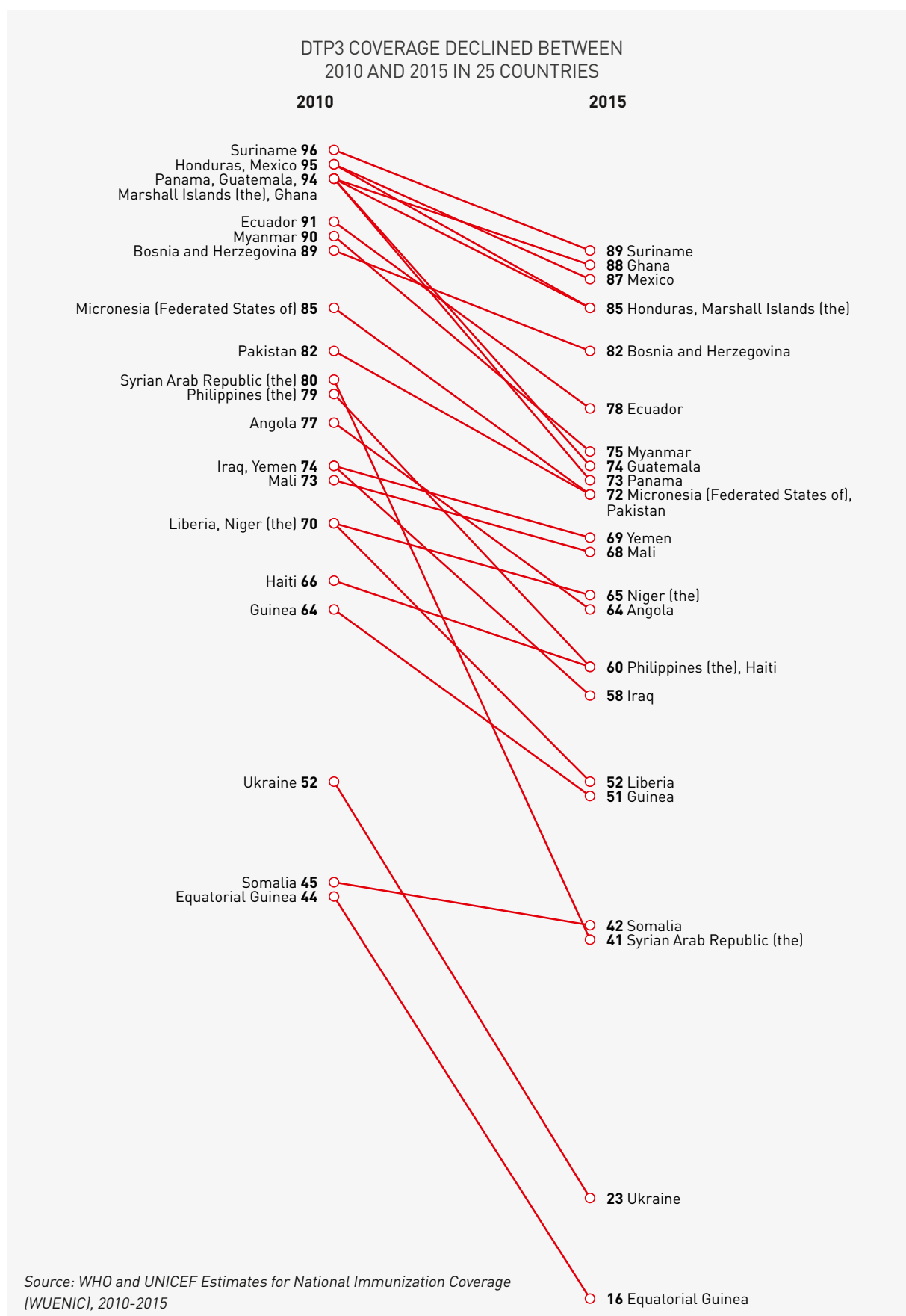
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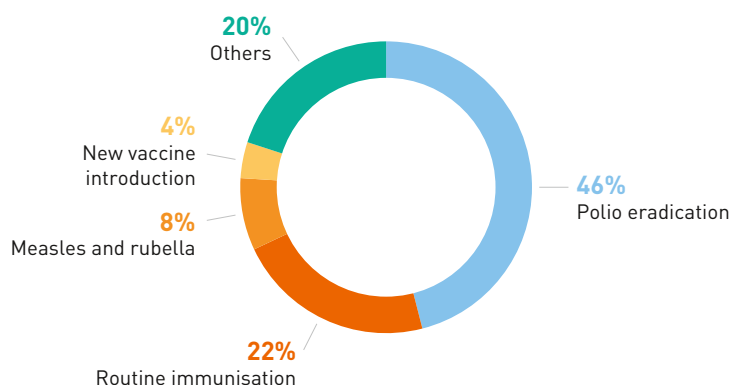
I 5. THREATS TO FUTURE PROGRESS

Looking ahead to the next four years, there are some key issues that pose a real threat to our ability to achieve GVAP goals and protect more lives through immunization.



Transitions. Polio transition planning is underway, and planners are grappling with how to manage the real consequences for routine immunization. Polio workers and resources frequently support new vaccine introduction planning, disease surveillance activities, routine immunization services and outbreak response. In DRC, for example, polio staff were pivotal in the country's rapid response to a recent yellow fever outbreak. Polio staff were also used in Nigeria to contain the spread of Ebola. Without polio-funded staff, equipment, and surveillance systems, immunization programmes will be left with critical gaps in human resources and other assets, which could greatly inhibit progress toward and sustainability of GVAP goals.

POLIO STAFF SPEND MORE THAN HALF THEIR TIME SUPPORTING OTHER IMMUNIZATION AND HEALTH SERVICES



Source: Boston Consulting Group study in Afghanistan, Angola, Chad, DR Congo, Ethiopia, India, Nigeria, Pakistan, Somalia, South Sudan for the Global Polio Eradication Initiative, 2015

Conflicts and emergencies. Conflicts and emergencies continue to be a concern, not just for communities living in fragile areas, but also for regions that are affected by large influxes of migrants and refugees. At the moment, host countries are required to locate, enumerate and vaccinate large populations that are either passing through or permanently relocating to the area. While some countries are making valiant efforts to manage the influx, others are quickly overwhelmed by the increased burden and cost.

Outbreaks. Disruptive and expensive outbreaks of vaccine-preventable diseases drain immunization resources and highlight inadequacies in both routine and supplemental immunization services. In 2015, large yellow fever, measles, and cholera outbreaks occurred in Africa, posing major challenges to immunization programmes in affected countries. Learning to manage outbreaks and simultaneously maintain immunization services will be key to building more resilient health systems that can withstand the strains of outbreaks and emerging diseases.

Without polio-funded staff, equipment, and surveillance systems, immunization programmes will be left with critical gaps in human resources and other assets, which could greatly inhibit progress toward and sustainability of GVAP goals

At the moment, host countries are required to locate, enumerate and vaccinate large populations that are either passing through or permanently relocating to the area

I 6. CAUSE FOR HOPE

Despite legitimate concerns, the SAGE sees many reasons to be hopeful that immunization will provide the cornerstone for health programmes around the world for decades to come.

Polio endgame. The world is on the cusp of polio eradication and can achieve it by applying what is already known to work and maintaining focus. Achieving polio eradication is validation that the global community can come together to achieve a common goal. The switch from trivalent OPV to bivalent OPV occurred across the globe within a fortnight, and this with the successful phased introduction of IPV, demonstrates the power of political will and the strength of good governance. If this can be achieved even in countries where systems are weak, then similarly immunization coverage can also be improved.

Success stories. Some countries are taking the power of immunization to heart and are reaping the benefits. They show us that achieving the GVAP is possible and that the impact is worth the investment and commitment. 17 countries made greater than 10% gains in coverage between 2010 and 2015 including highly populated countries like the Democratic Republic of Congo, Ethiopia and India. Still others, like Mexico and Uganda, took risks to change systems and improve outcomes for the better even if the payoff is still to come. Their stories offer lessons, new ideas and proven strategies for improving performance in different environments.

Return on investment. As reported in a recent article in Health Affairs, immunization with ten common antigens yields a 16:1 net return on investment in low- and middle-income countries during the Decade of Vaccines (2011 – 2020).³ Factoring the value that people place on living longer and healthier lives, the return almost triples. Few other health intervention are as effective at minimizing the impacts of morbidity and mortality and ensuring good health and well-being for families everywhere.

Ripple effect. Immunization is a critical component of the health system without which universal health care cannot be realized. It is often a child's first contact with the health system and a potential platform for integrated preventive care from infancy through adulthood. The SAGE recently recommended using the Composite Coverage Index⁴ to measure integration of health services. This indicator will be used to identify missed opportunities across four platforms of health services: immunization, family planning, maternal/newborn care, and case management of a sick child. The indicator already shows that immunization is an underused platform for delivering other critical health services along the life course.

Unlocking further potential. Research and development efforts are accelerating the discovery and testing of an expanded portfolio of vaccine candidates against malaria, HIV, tuberculosis, influenza and RSV, among others. Platform delivery technologies are also being developed to make immunization easier to safely store, transport, and deliver. These technologies, tested, licensed and deployed at scale will have a powerful impact on health and well-being around the world.

Some countries are taking the power of immunization to heart and are reaping the benefits. They show us that achieving the GVAP is possible and that the impact is worth the investment and commitment

Immunization is an underused platform that can be leveraged to deliver other critical health services along the life course

³ Ozawa S, et al. Return on Investment from Childhood Immunization in Low- and Middle-Income Countries, 2011-20. Health Affairs 35: 199-207, No. 2, Feb 2016. Available from: URL: <http://dx.doi.org/10.1377/hlthaff.2015.1086>

⁴ Composite Coverage Index: <http://www.countdown2015mnch.org/about-countdown/countdown-data>

7. WHY IMMUNIZATION MATTERS NOW MORE THAN EVER

Individuals. Immunization has proven potential to improve the health and well-being of individuals and family units, in all their forms. Vaccines are now available throughout the life course, protecting against some of the most common causes of death for children under five as well as for diseases that come later in life, including two forms of cancer (liver and cervical cancer).

Communities. As populations become increasingly urbanized and as conflicts and emergencies result in large population migrations, immunization programmes with high and equitable coverage have great potential to protect the world's most vulnerable from illness, disability and death.

Health systems. Immunization is a core component of Universal Health Care. It provides a foundation of infrastructure and staff, systems and tools that can expand the reach of all preventive services. At a time when health systems are under pressure, opportunities for the integration of immunization services must be actively sought. Immunization is a fundamental strategy to achieve other health priorities, from controlling viral hepatitis, to curbing antimicrobial resistance, to providing a platform for adolescent health and improving antenatal and newborn care.

Health security. Now more than ever we need health systems that are resilient and able to withstand—and even facilitate the control of—emerging diseases, outbreaks and other threats to health security. Immunization systems that are strong and resilient can be used to manage threats to health security and can more easily recover from such threats.

Sustainable development. Immunization is a key driver of sustainable development, enabling other development priorities such as education and economic development to take hold.

Immunization is a fundamental strategy to achieve other health priorities, from controlling viral hepatitis, to curbing antimicrobial resistance, to providing a platform for adolescent health and improving antenatal and newborn care

I 8. SAGE RECOMMENDATIONS

Four years ago at the World Health Assembly, all 194 Member States agreed to the goals of the Global Vaccine Action Plan (GVAP). These goals give focus and urgency to the Decade of Vaccines; their achievement will have a resounding impact on health. Not only do strong immunization programmes prevent disease, they facilitate compliance with international health regulations; contribute to the control of anti-microbial resistance; prevent outbreaks and provide an avenue for outbreak response; and contribute to sustainable development.

THE SAGE RECOMMENDS THAT MEMBER STATES:

1. Demonstrate stronger leadership and governance of national immunization systems.

- a) Ministers of Finance, Ministers of Health, and other line ministries at all levels must be stronger immunization advocates within their countries and regions, conveying the value and urgency of investing in and sustaining immunization programmes as part of all government-supported health packages, including Universal Health Care.
- b) Governments are encouraged to enact laws that guarantee access to immunization, establish functional National Immunization Technical Advisory Groups, ensure that sufficient budgets are allocated to immunization each year and create mechanisms to monitor and efficiently manage funds at all levels (including those from private sector).
- c) National leaders must take courageous decisions to initiate necessary upgrades to systems, protocols, and policies that might be limiting immunization programmes. Such upgrades might require redesigning supply chains, information systems and procurement policies, and reassessing roles and responsibilities after decentralization of the health system.
- d) National immunization programme managers should report each year to their National Immunization Technical Advisory Group on progress made, lessons learnt and remaining challenges toward implementing National Immunization Plans and show how these plans are aligned to Regional and Global Vaccine Action Plan goals. Country progress reports should be shared and discussed with Regional Committees during a dedicated session on immunization as stated in the WHA resolution (WHA 65.17).

2. Prioritize immunization system strengthening.

- a) Countries should expand immunization services beyond infants and children to the whole life course, and determine the most effective and efficient means of reaching other age groups within integrated health service provision. New platforms are urgently needed to reach people during the second-year-of-life, childhood, adolescence, pregnancy, and into adulthood.
- b) The 34 countries with DTP3 national coverage levels below 80% are requested to accelerate the implementation of proven interventions to strengthen immunization systems as part of integrated health services. Priority interventions should include: human resource development; regular strategic and operational planning; micro-planning to reach the unreached; more effective vaccine management; and the collection and use of data for monitoring and decision-making.

While the GVAP goals are ambitious, many countries, including some of the most resource-constrained, have capitalized on the health and economic benefits of vaccines and shown that achieving the GVAP goals within the Decade of Vaccines is not only possible, but necessary

3. Secure necessary investments to sustain immunization during polio and Gavi transitions.

- a) All countries should mitigate any risk to sustaining effective immunization programmes when polio funding decreases. All Member States with large polio staff and resources are requested to describe in their polio transition plans how they propose to maintain and fund critical immunization, laboratory and surveillance activities that are currently supported with polio funding or staff.
- b) Countries transitioning from Gavi support must advocate strongly and persistently for increased domestic financing to sustain immunization gains over time.
- c) Immunization donors must also look beyond their investments in Gavi to ensure that Gavi-transitioning and self-supporting countries as well as countries facing large decreases in polio funding have the necessary capacity, tools and resources to sustain immunization over the long term.

4. Improve surveillance capacity and data quality and use.

- a) All countries should strengthen and sustain their surveillance capacity by investing in disease detection and notification systems, routine analysis and data reporting systems, stronger laboratory capacity and a clear process for investigating and confirming cases, and responding to and preventing outbreaks.
- b) Decision makers at all levels of the immunization programme are requested to use up-to-date immunization-related data (e.g., disease surveillance, coverage, and programme delivery data) to guide programmatic and strategic decisions that reduce disease and protect targeted populations.

THE SAGE RECOMMENDS THAT IMMUNIZATION PARTNERS:

5. Enhance accountability mechanisms to monitor implementation of Global and Regional Vaccine Action Plans.

- a) The leaders of GVAP secretariat agencies and global immunization partners should advocate forcefully and consistently in national and international fora for the urgency and value of accelerating the pace of global progress toward achieving the GVAP goals by 2020.
- b) Civil Society Organizations should describe how their work maps against different national immunization plans in their 2017 GVAP report, so that the geographic and programmatic scope of their work is more visible. Where possible, CSOs should also measure and share the impact of their work.

6. Achieve elimination targets for maternal and neonatal tetanus, measles and congenital rubella syndrome.

The Maternal and Neonatal Tetanus and Measles and Rubella Initiatives are each requested to develop an investment case that specifies the additional funding that is required to achieve and sustain elimination targets in routine immunization programmes and use the investment case to solicit necessary support from donors and national governments by the end of July, 2017.

7. Resolve barriers to timely supply of affordable vaccines in humanitarian crisis situations.

International agencies, donors, vaccine manufacturers and national governments must work together to alleviate the financial burden placed on countries with large migrant and refugee populations and ensure a timely supply of affordable vaccines in humanitarian crisis situations.

THE SAGE RECOMMENDS THAT VACCINE RESEARCH AND DEVELOPMENT PARTNERS:

8. **Support vaccine R&D capacity in low- and middle-income countries.**

- a) Continue supporting the expansion of regulatory capacity and clinical trial capacity by building upon models like the African Vaccine Regulatory Forum and the Developing Country Vaccine Regulators' Network, accelerating regulatory pathways for vaccines in emergency settings, and insisting on compliance with the existing WHO position to register clinical trials and report results in a timely manner.
- b) WHO and the Product Development for Vaccines Advisory Committee (PDVAC) should continue developing global, consensus-based strategic goals and prioritizing R&D for vaccines and delivery systems that address unmet needs in low- and middle-income countries.
- c) Researchers should support the development of high-quality, standardised animal models, standardized assays and human challenge models to streamline product development and provide better-quality information for product advancement decisions.

9. **Accelerate the development and introduction of new vaccines and technologies.**

Researchers and investigators, worldwide, should accelerate the development of priority new vaccines and technologies from R&D to full-scale use. This will require that implementation research occur during clinical trials to reduce the delay between regulatory, financing and programmatic decisions.

ANNEX 1: STRATEGIC ADVISORY GROUP OF EXPERTS ON IMMUNIZATION (SAGE) DECADE OF VACCINES WORKING GROUP MEMBERSHIP

SAGE MEMBERS

- Narendra Arora (Chair of the Working Group), Executive director, International Clinical Epidemiology Network, India (SAGE Member from 2010 – 2016)
- Yagob Al-Mazrou, Secretary General - Health Services Council of the Kingdom of Saudi Arabia, Saudi Arabia
- Alejandro Cravioto, Independent consultant, Mexico

EXPERTS

- Marie-Yvette Madrid, Independent Consultant, Geneva, Switzerland
- Amani Mahmoud Mustafa, Project Manager, Sudan Public Health Training Initiative, The Carter Center, Sudan (affiliation as of May 2014 and previously EPI Manager, Ministry of Health, Sudan).
- Rebecca Martin, Director of the Center for Global Health, US CDC, USA
- Helen Rees, Executive Director - Reproductive Health Research Unit, University of Witwatersrand, South Africa (former SAGE Chair 2010 - 2013)
- David Salisbury, Associate Fellow, Centre on Global Health Security, Chatham House, London, UK (previously Director of Immunization, Department of Health, UK and former SAGE Chair 2005 - 2010)
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- Jon Kim Andrus, Executive Vice President and Director of Vaccine Advocacy and Education, Sabin Vaccine Institute, Washington, DC, USA
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- Budihardja Singgih, Technical Director Program Australia Indonesia Partnership for Health Systems Strengthening, Jakarta, Indonesia
- Qinjian Zhao, Associate Dean, School of Public Health, Xiamen University, Xiamen, Fujian, China.

WORKING GROUP SECRETARIAT

- Bill & Melinda Gates Foundation
- Gavi, the Vaccine Alliance
- United States National Institute of Allergy and Infectious Diseases
- United Nations Children's Fund
- World Health Organization

EXPANDING THE POTENTIAL OF THE HEPATITIS B VACCINES BY OPTIMIZING THE IMMUNIZATION SCHEDULES AND DELIVERY STRATEGIES

A. POLICY QUESTIONS AND OVERALL CONCLUSIONS

A safe and effective vaccine against hepatitis B has been available since 1982. The vaccine has also been associated with reductions in the incidence and mortality from hepatocellular carcinoma (HCC) in time series analyses. By 2015, 185 (95%) of countries worldwide had introduced the hepatitis B vaccine with 97 (49%) countries having introduced the recommended birth dose. WHO has estimated that 84% of infants received at least three doses of Hepatitis B containing vaccine in 2015 and 39% of newborns received the birth dose.

Number of doses

Evidence available supports current recommendation of at least 3 doses of vaccine. The current recommendation is that the birth dose should be followed by 2 or 3 doses to complete the primary series. In most cases, one of the following 2 options is considered appropriate: (i) a 3-dose schedule of hepatitis B vaccine, with the first dose (monovalent) being given at birth and the second and third (monovalent or combined vaccine) given at the same time as the first and third doses of DTP vaccine; or (ii) 4 doses, where a monovalent birth dose is followed by 3 monovalent or combined vaccine doses, usually given with other routine infant vaccines.

For recombinant DNA vaccines there is no difference in the proportion of infants becoming seroprotected 1-3 months post-vaccination with a birth dose followed by 3 primary doses (b0+3p) vs. a birth dose followed by 2 primary doses (b0+2p). Also, the proportion seroprotected between a birth dose followed by 3 primary doses (b0+3p) vs. no birth dose + 3p doses is similar. For all other comparisons, schedules with a higher number of doses seem to increase the rate of seroprotection, but these results were based on a few studies of limited quality. There is some evidence indicating that vaccination schedules with a higher number of doses and possibly a birth dose were associated with higher antibody concentrations (GMCs) at 1-3 months post-vaccination.

Age at administration of first dose

Current recommendation is that all infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours. There is moderate quality evidence to support the effectiveness of hepatitis B vaccine given within 24 hours of birth to prevent hepatitis B infection.

Interval between doses

Current recommendation is that the birth dose should be followed by 2 or 3 doses with a minimum interval of 4 weeks. Available evidence is inconclusive regarding the differences in immunogenicity for various intervals between doses (e.g. 4 or 8 weeks apart). For recombinant DNA and plasma vaccines there is a higher proportion of infants becoming seroprotected 1-3 months post-vaccination with 1-3 months or 1-2-7 months schedules when compared to 3-5 and 1-3-10 months schedules respectively; this evidence is based on few studies of limited quality. There is very low quality evidence that recombinant DNA vaccine given in the 3-5-11 months schedule resulted in higher antibody concentrations (GMCs) measured 1-3 months post vaccination when compared to a 2-4-6 months schedule.

This summary includes

1 Policy questions

4 Key Findings

4 Burden of disease

3 Epidemiology of HBV infection

8 Effect of number of doses

11 Effect of age at administration of first dose

14 Effect of the interval between primary doses

16 Effect of booster dose

16 Catch up vaccination

19 Low birth weight infants

21 HIV infected population

22 Long term protection

22 Vaccination of HCW

22

Thermostability of hepatitis B monovalent vaccines

24 Barriers to introduce the birth dose

27 Economic Evaluation of Hepatitis B vaccination

31 Prevention of Mother to child transmission

31 Countries that have introduced and Hepatitis B birth dose

Booster dose

There is no evidence to support the need for a booster dose of hepatitis B vaccine in routine immunization programmes. For recombinant DNA HBV vaccines, there is low quality evidence on higher immunogenicity, however, the clinical relevance of these findings is unknown. The comparison of 3 or 4 primary vaccination schedules with an additional booster dose at 5 years of age vs. no booster added showed a very low quality evidence indicating higher proportion of seroprotection of a booster dose of recombinant DNA vaccine given 5 years after 3 or 4 primary doses when compared to no booster in children, this effect last for at least 3 years. There was also a very low quality evidence indicating that a booster dose of recombinant DNA vaccine given 5 years after 4 primary doses gives higher antibody concentrations (GMCs) measured 1-15 years post vaccination.

Catch up vaccination

There may be no difference in the proportion of children and adolescents becoming seroprotected 1-3 months post-vaccination when 2 primary catch-up doses are compared with 3 primary catch-up doses; these results remained consistent after a longer follow-up period 12 years. At 22 years in one study, seroprotection was higher with 3p than with 2p; however, follow-up was very low (<20%), and it is not possible to draw conclusions on this results. There is some evidence indicating that catch-up vaccination schedules with 3 doses were associated with higher antibody concentrations (GMCs) at 1-3 months post-vaccination and at longer follow-up periods when compared with 2 primary catch-up doses.

Immunization of LBW newborns

Current recommendation is that preterm infants should be vaccinated at birth and subsequently enters the national hepatitis B vaccination schedule. However, if an infant's birth weight is <2000 g, the vaccine dose given at birth should not be counted towards the primary series and 3 additional doses should be given according to the national vaccination schedule. Current data suggest that all babies should have a birth dose whatever their birth weight and those with a low birth weight should start their primary series of vaccination 1 month later or soon later after the birth dose (e.g. at the age of the national recommended schedule for the first dose).

Immunization of HIV infected population

There is no reason to change the current WHO recommendation of vaccination of HIV positive individuals as early as possible. There is no clinical evidence on the benefits of providing an additional dose or a dose with higher titre to HIV infected individuals. Higher titre doses do not result in longer term protection compared to standard doses.

What is the impact of the vaccination programme in the hepatitis B epidemiology?

Infant HBV vaccination achieves substantial protection against chronic carriage in early adulthood, even though approximately a quarter of vaccinated young adults have been infected. This protection persists past the potential onset of sexual activity and suggests no need for a booster dose.¹ A study in the Gambia² found that 60.9% of the children who became chronic carriers despite having been fully vaccinated had HBsAg-positive mothers and none received the birth dose. These findings suggest the importance of interrupting mother to mother transmission to reduce the HBV-related burden.

Several clinical trials have shown that a timely birth dose may reduce by 60 to 80% the likelihood to become a chronic HBsAg carrier compared to no birth dose. A model estimated the burden of HBV in terms of HBV-attributable acute

31 List of WHO Prequalified HBV vaccines

31 Hepatitis B Schedules

31 Number of births occurring at home

31 Number of births attended by skilled persons

32 References

X THIS

SUMMARY DOES NOT INCLUDE DETAILED INFORMATION ON OPERATIONAL ISSUES

and chronic disease outcome, and the impact of the global vaccination efforts at reducing HBV related disease, both at the current time, and into the future.

Does the available evidence support flexibility in the requirement for cold chain storage of Hepatitis B monovalent vaccines in order to expand the delivery of the birth dose?

Since access to the birth dose may be hampered by an important proportion of deliveries at home or limited cold chain in peripheral health, a review of published data and manufacturers' data assessed the thermostability of Hepatitis B monovalent vaccine. Existing data indicates that most hepatitis B vaccines are heat stable and have been found to maintain immunogenicity after exposure to temperatures of up to +45°C for one week and temperatures up to +37°C and +41°C for several weeks. Field experience suggest that there may be programmatic advantages in keeping hepatitis B vaccine in ambient temperatures at service delivery points for a priori determined periods (e.g. one week), especially as a strategy for reaching home births. This indicates that these vaccines would be able to meet the CTC storage of at least 3 days at at least 40°C and these manufacturers should be encouraged to seek on-label extended controlled temperature chain.

Annex 1 includes conclusions and recommendations of the ad-hoc expert consultation on Hepatitis B vaccines (1-2 September 2016).

Type of evidence: randomized clinical trials (RCTs), observational studies, mathematical model estimates

Quality: Varies across studies. Not formally assessed for the mathematical model.

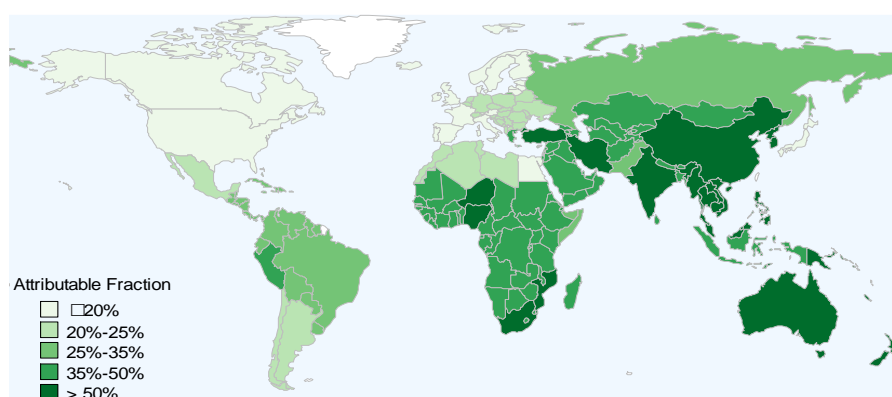
Caution: For some of the comparisons discussed the evidence is considered low quality because there is a limited number of trials or because they are afflicted with high risk of bias.

B. KEY FINDINGS

Burden of HBV disease

A systematic review estimated the global burden of liver cancer attributable to HBV and HCV. The estimation proceeded in three steps: 1) extrapolation of prevalence estimates to countries without data; 2) calculation of country-specific AF by combining estimates of prevalence and relative risk; 3) combination of AF with estimates of cancer burden and aggregation to regional estimates of cancer attributable to HBV and HCV. HBV and HCV are responsible for 72% of liver cancer cases worldwide, with wide geographical variations in the attributable fraction. For further information refer to WHO HBV burden 2016 document.

Figure 1: Estimated fraction of liver cancer attributable to Hepatitis B by country
Plummer et al 2016³



Epidemiology of Hepatitis B infection

Assessment of the global and regional prevalence of HBV carriage.

In September 2015, the United Nations General Assembly adopted the 2030 Agenda for Sustainable Development. A goal is to eliminate viral hepatitis as a public health threat by 2030. The target for 2020 is a 1% prevalence of HBsAg among children⁴.




A systematic review of published seroprevalence data that also considered the date of Hepatitis B vaccine introduction, was used to update the global estimates of hepatitis B surface antigen seroprevalence⁵. Table 1 below depicts the countries according to the proportions seropositive in children. It is important to note that for some countries the data is from nationally representative surveys, while for others data is from local samples. Control of early childhood transmission of Hepatitis B control have had important advances in several regions around the world. The Western Pacific is the region where it has been documented more extensively using national serosurveys. Among the most populated countries in the area, only Philippines and Papua New Guinea remain with more than 2% of HBsAg in children under 5 years. Some small territories still lack adequate information. In Eastern Mediterranean, most countries have met the goal of less than 2% of HBsAg, some have been confirmed using national or local serosurveys in children and others, because national general prevalence do not support a higher prevalence in children. That is the case of Bahrain, Iran, Kuwait and others. That is also the case for South East Asia where only Nepal has a national serosurvey. However local studies from other lower intermediate endemic countries, like India and Bangladesh, supports that prevalence in children is decreasing. In Africa, most countries do not have enough information on prevalence among vaccinated children. In some of them, local studies show that prevalence in children born after vaccine introduction is going down. Europe and Americas are regions where infection in early childhood are low. In addition many countries in Europe and almost all in Latin America have been vaccinating for two or three decades. Some countries in both regions lack enough data to be classified and therefore should be encouraged to conduct additional studies.

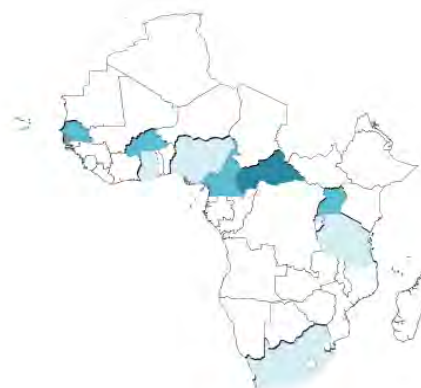
Table 1a: Preliminary estimates of levels of endemicity in children < 5 years of age by WHO region using published literature⁵




WHO Region	Countries with HBsAg prevalence < 1% in children < 5 yrs	Countries with HBsAg prevalence 1-2% in children < 5 yrs	Countries with HBsAg prevalence > 2% in children < 5 yrs	Countries with no data
Western Pacific	China*, Macao*, Hong Kong*, Malaysia*, Mongolia*, Rep of Korea*, Am Samoa*, Australia*, Brunei*, Cook Islands*, Japan*, New Zealand*, Palau*,	Tonga*, Cambodia*, Fiji*, Lao PDR*, Marshall Is*, N Mariana Is*, Vietnam*,	Papua New Guinea*, Kiribati*, Philippines*, Samoa*, Solomon Is*, Vanuatu*	Fr Polynesia, Guam, Micronesia, Nauru, N Caledonia, Niue, Tokelau, Tuvalu, Wallis and Futuna
Africa	Uganda**, Cameroon**, Burkina Fasso**, Gambia*, Senegal**, Seychelles, South Africa*	Tanzania**, Rwanda**, Madagascar, Kenya, Burundi, Algeria, Cape Verde, Ethiopia, Eritrea,		Nigeria, Ghana, Niger, Angola, South Sudan, Mozambique, Zimbabwe, Malawi, Namibia, Botswana, Swaziland, Congo, Guinea, Guinea Bissau, Equatorial Guinea, Sierra Leona, Cote d'Ivoire, Togo, Benin,
Eastern Mediterranean	Bahrain, Iran, Jordan, Kuwait, Lebanon, Libya*, Morocco, Oman*, Palestine, Qatar*, Saudi Arabia, Tunisia, United Arab Emirates, Egypt*	Syria, Afghanistan**, Iraq, Yemen**, Djibouti	Somalia, Pakistan, Sudan,	
South East Asia	Nepal*, Sri Lanka, Bangladesh*, India**, Indonesia**	, Thailand**		Bhutan, Myanmar,
America	USA*, Canada, Mexico*, Peru**, Venezuela*, Costa Rica, Panama, Colombia**, Ecuador, Argentina, Brazil**, Uruguay, Paraguay, Cuba, Guatemala, Nicaragua			Haiti, Belize, Dominican Republic, Jamaica, Surinam
Europe	Austria, Belgium, Bosnia, Czech Rep, Denmark, France, Germany, Greece, Hungary, Iceland, Ireland, Israel**, Lithuania, Netherlands, Norway, Poland, Portugal, Serbia, Slovakia, Slovenia, Spain, Switzerland, Ukraine, UK, Turkey, Russia, Italy**, Bulgaria**	Azerbaijan, Cyprus,	Tajikistan, Albania**	Romania, Moldova, Kyrgyzstan, Kosovo, Kazakhstan, Belarus, Georgia

* based on national seroprevalence surveys
 ** based on local seroprevalence studies
 based on general prevalence studies




Figure 1b: Countries with evidence of HBsAg prevalence among vaccinated cohorts.

AFRO			
Country	Year of Vaccine Introduction	Prevalence	Reference
< 1% 			
Uganda	2002	0%	Teshale 2015
Senegal	2004	0.3%	Bekondi 2015
South Africa	1995	0.4%	Schoub 2002
Burkina Faso	2006	0.5%	Ouedraogo H 2013
Cameroon	2005	0.7%	Cuille 2013
1-2 % 			
Rwanda	2002	1%	Orikiiriza 2015
Tanzania	2002	1%	Muro 2013
Nigeria	2004	1.3%	Odusanya 2005
Gambia	1995	<1.5%	Peto 2014
Ghana	2002	1.5%	Dassah 2015
2-5 % 			
Central Africa Republica	2008	5%	Cuille 2013






AMRO			
Country	Year of Vaccine Introduction	Prevalence	Reference
< 1% 			
Peru	2005	0%	Cabezas 2014
Brazil	1998	<1%	Ximenez 2015
1-2 % 			
Bolivia	2000	5% AntiHBc (1% HBsAg)	Masuet-Aumatell C 2013
2-5 % 			
Colombia	1994	2%	De la Hoz 2008





EURO			
Country	Year of Vaccine Introduction	Prevalence	Reference
< 1% 			
Tajikistan	2002	<1%	Khetsuriani 2015
1-2 % 			
Bulgaria	1991	1%	Kevoorkyan 2015
2-5 % 			
Uzbekistan	2001	2%	Kurbanov 2010



EMRO			
Country	Year of Vaccine Introduction	Prevalence	Reference
< 1% 			
Iran	1993	0%	Saffar H 2014
Egypt	1992	0.5%	Salama I 2013
Oman	1990	0.5%	Al Awaidy 2013
Libya	1998	< 1%	Daw 2014
1-2 % 			
Tunisia	1995	1%	Chaoouch H 2016
Saudi Arabia	1989	< 1.5%	Al Humayed 2016
2-5 % 			
Yemen	1999	2.7%	Sallam 2012
Afghanistan	2006	3.6%	Tanju I 2014



SEARO			
Country	Year of Vaccine Introduction	Prevalence	Reference
< 1% 			
Bangladesh	2005	0%	Paul 2012
Indonesia	2003	0%	Utsumi 2014
Nepal	2005	0.1%	Raj Upreti 2014
India	2011	0.15%	Aggarwal 2014
1-2 % 			
Thailand	1992	1%	Posuwan 2016



WPRO			
Country	Year of Vaccine Introduction	Prevalence	Reference
< 1% 			
Cook Islands	1989	0%	Wiesen2016
Macao	1989	0%	Wiesen2016
Palau	1988	0%	Wiesen2016
Guam	N/A	0%	GuamHealth Dpt2015
Niue	1986	0%	NiueHealth Dpt 2015
Brunei Darussalam	1988	0.1%	Wiesen2016
American Samoa	1986	0.2%	Wiesen2016
New Zealand	1985	0.2%	Wiesen2016
China	1992	0.3%	Wiesen2016
Malaysia	1989	0.3%	Cheang 2013
Singapore	1987	0.3%	Wiesen2016
Australia	2000	0.4%	Gidding 2007
Republic of Korea	1995	0.4%	Wiesen2016
Mongolia	1991	0.5%	Wiesen2016
Philippines	1992	<0.5%	Balangue-Tundag 2015
Hong-Kong	1988	0.8%	Wiesen2016
Wallis and Futuna	N/A	0.9%	Wiesen2016
1-2% 			
Mongolia	1991	1%	Ochirbat 2008
Singapore	1987	1%	Ang 2013
Fiji	1995	1.3%	Tsukakoshi 2015
Cambodia	2006	1.5%	Bunsoth 2013
Laos	2004	1.7%	Xeuatongsa 2014
2-5 % 			
Papua NG	1989	1.4-3.2%	Kitau 2015
Marshall I and Micronesia	1988	1.8%-2.5%	Bialek 2010
Laos	2004	2%	Komada 2015
VietNam	2003	2.2%	Wiesen2016
Laos	2004	3%	Black 2014
Kiribati	1995	3.3%	Patel 2016
Malaysia	1989	5%	Hudu 2013*



Figure 1A continuation

Global and country-specific estimates

Modelling of HBV infection seroprevalence globally⁶

The objective was to generate and provide up to date estimates on the global, regional and national prevalence of chronic HBV infection measured by HBsAg prevalence in sera. This work is part of a wider study on estimating the impact of hepatitis B vaccination. The model benefits from inputs from a number of systematic reviews on HBV vaccine efficacy and on surface antigen (HBsAg) carriage. The statistical and modelling component of the work consists of three related subcomponents: (1) Estimation of the pre- and post-vaccination country-specific prevalence of HBsAg by age and sex using spatially explicit statistical models. This uses the systematic review of HBsAg prevalence and uses Bayesian statistical methods to infer estimates for settings (and age groups) where data are currently missing; (2) Country-specific estimates of the impact of HBV vaccination on severe HBV-related disease (in particular liver cancer and cirrhosis) using a static model. The model uses data from the HBsAg review and WHO data on HBV vaccine coverage by birth cohort. It takes account of horizontal and perinatal infection in childhood and has been fitted to data from a number of sources on progression to severe outcomes. It also takes account of past and projected future demographic changes to estimate the number of deaths prevented by HBV vaccination by country; (3) Detailed estimates of the impact of vaccination, including the indirect (herd immunity) impact are made using data from three countries with high quality pre- (and post-) vaccination data on HBsAg prevalence and HCC (China, The Gambia and South Korea). See detailed report in supplemental information online.

Does the emerging evidence suggest the need to adjust current Hepatitis B vaccine recommendations?

WHO Recommendations for Routine Immunization⁷

Since perinatal or early postnatal transmission is an important cause of chronic infections globally, all infants should receive their first dose of hepatitis B vaccine as soon as possible (<24 hours) after birth even in low-endemicity countries. The primary hepatitis B immunization series conventionally consists of 3 doses of vaccine (1 mono-valent birth dose followed by 2 monovalent or combined vaccine doses at the time of DTP1 and DTP3 vaccine doses). However, 4 doses may be given for programmatic reasons (e.g. 1 monovalent birth-dose followed by 3 monovalent or combined vaccine doses with DTP vaccine doses), according to the schedules of national routine immunization programmes. Premature low birth weight (<2000g) may not respond well to vaccination at birth. However, by 1 month of chronological age, premature infants, regardless of their initial weight or gestational age at birth, are likely to respond adequately. Therefore, doses given to infants <2000g should not be counted towards the primary series. (http://www.who.int/immunization/policy/Immunization_routine_table2.pdf)

Available evidence suggest that the current recommendations do not need to be adjusted. A systematic review by Soares et al⁸ included 72 studies (92 references) covering immunological and clinical outcomes (HBsAg, anti-HBs, anti-HBc, chronic HBV infection, serious adverse events, and all cause-mortality) for the following comparisons: timing of birth dose, number of doses after the birth dose, different intervals used for the same number of doses, timing of booster doses. All analyses were stratified by endemicity and time point of blood collection: regional endemicity has not directly impacted the results presented for any of the comparisons. Many studies were of poor methodological quality as reported.

There is a high flexibility of schedule possible in terms of number of doses and spacing provided the first two doses were delivered in early life.

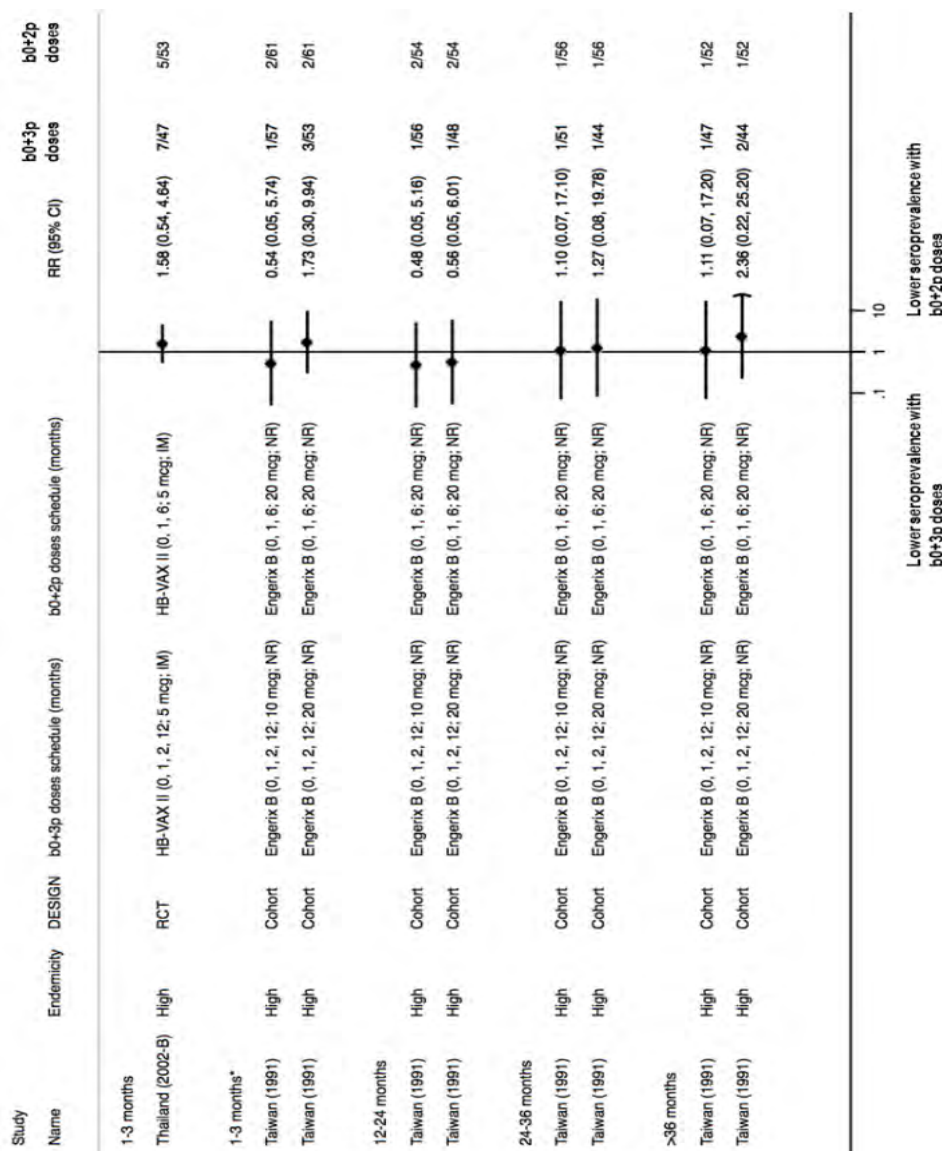
Effect of number of doses of Hepatitis B vaccine on selected outcomes:

Available evidence suggest that the current recommendations do not need to be adjusted. A systematic review⁸ found that schedules with a higher number of doses seems to increase the rate of seroprotection for b0+3 v 3p and b0+1p v b0+2p in high endemicity areas. There seemed to be no difference in the proportion of infants becoming seroprotected 1-3 months post-vaccination for all other comparisons. These results are based on a few studies of limited quality. There is some evidence indicating that vaccination schedules with a higher number of doses and possibly a birth dose were associated with higher antibody concentrations (GMCs) at 1-3 months post-vaccination. There were very few data on clinical effectiveness provided for a higher number of doses against chronic hepatitis B carriage. There was no difference in the number of serious adverse events when comparing different schedules. There was no data available on the effect of hepatitis B vaccination and all-cause mortality. The quality of evidence for these comparisons is very limited.

Table 2: Summary of findings per outcome of the number of doses of recombinant DNA HBV vaccine

Outcome of interest	Number of doses		Birth dose + 3p vs 3p	3 primary vs 2 primary doses
	Birth dose + 3p vs birth dose + 2p			
HBsAg seroprevalence	Very low quality evidence. One RCT ⁹ and one cohort ^{10 11} study provided data for multiple time points. Both studies were in high endemicity areas. Mothers in both studies were HBeAg + and were HBsAg + in one study. There was no evidence of a difference in seropositivity rates between schedules at any of the time points for the two studies with different methodological design.	None of the included studies assessed this outcome.	There were no studies found that assessed this outcome	
	Moderate quality evidence from RCTs Three RCTs ^{9 12 13} provided data on this comparison. Mothers were HBsAg and HBeAg positive in one study. There is probably little or no difference between b0 + 3p vs. b0 + 2p recombinant DNA HBV vaccines on Anti-HBs seroprotection at 1-3 months, 3-6 months or 6-12 months post vaccination. Very low quality evidence Three cohort studies ^{10 11 14 15 16 17 18 19} showed no evidence of a difference in seroprotection rates between schedules at 1-3 months after immunization, 6-12 months and 24-36 months. One study ¹⁴⁻¹⁸ showed higher seroprotection with b0+3p than b0+2p at 12-24 months (RR 1.13, 95% CI 1.02, 1.26) and >36 months follow-up (RR 1.15, 95% CI 1.02, 1.29), for schedules in which HBIG was given at birth. However, results are consistent with RCTs.	Low endemicity – very low quality evidence One low endemicity cohort study ²⁰ , found no evidence of a difference in seroprotection rates between a birth dose + 3p compared to a 3p doses. Moderate endemicity - low quality evidence one moderate endemicity quasi-RCT ²¹ found no evidence of a difference in seroprotection rates between a birth dose + 3p compared to a 3p doses. High endemicity – moderate quality evidence Three high endemicity RCTs ^{22 39 23} found marginally statistically significant higher seroprotection rates (RR 1.05, 95%CI 1.02-1.07) between a birth dose + 3p compared to a 3p doses	Very low quality from cohort studies One cohort study ²⁴ in a low endemicity area found that there was no difference in seroprotection rates at 1-3 months after immunization; at >36 months.	

Outcome of interest	Number of doses		
	Birth dose + 3p vs birth dose + 2p	Birth dose + 3p vs 3p	3 primary vs 2 primary doses
GMCS of anti-HBs	<p>Very low quality evidence</p> <p>Two RCTs^{25 13,19} and one cohort study¹⁴⁻¹⁸ Results at 1-3 months after vaccination were very heterogeneous with one RCT in low endemicity region (Netherlands 1993-A) favouring the b0+3p schedule, WMD in log GMCs of 1.22 (95% CI 0.59, 1.85); this corresponds to a GMC ratio of 3.39 (95% CI 1.80-6.34) which indicates that the b0+3p schedule gave higher antibody concentrations 1-3 months post vaccination compared to the b0+2p schedule. Whereas, one RCT in a high endemicity region (Malaysia 2008) showed no difference between the two schedules at 1-3 and 6-12 months.</p> <p>A cohort study from a high endemicity region (Thailand 2002-A) showed no difference at 1-3 months after vaccinations, but showed results favouring the b0+3p schedule in the low endemicity region at 12-24, 24- 36 and above 36 months.</p>	<p>Moderate quality evidence</p> <p>Two RCTs^{38,21} from low and moderate endemicity areas and two RCTs^{39,22} from high endemicity areas found that the birth dose + 3 primary doses schedules probably improves GMCs compared to 3 primary doses only.</p>	<p>Low quality evidence</p> <p>One RCT¹³ in high endemicity area and one cohort study²⁴ in a low endemicity area found no significant difference in the antibody concentrations (GMCs) at 1-3 months in the high endemicity study; higher antibody titres were shown in the 2p group at 6-12 months post-vaccination.</p> <p>In the cohort study, higher antibody titres were seen with the 3p schedule when a 1, 3 month schedule was compared with a 1, 2, month schedule.</p>



Effect of timing of first dose of Hepatitis B vaccine on selected outcomes

One RCT²⁶ of moderate quality evidence comparing recombinant DNA HBV vaccine at 0, 1, 2 and 14 months vs placebo among children born to HBsAg positive mothers found anti-HBs antibodies in protective titers in 76.7% of children aged 4-5 months after the third dose. Another four RCTs^{27 28 29 30 31 32} of moderate quality evidence using plasma derived vaccine compared a birth dose + 3p doses or a birth dose + 2p versus placebo concluded that HB vaccine should be provided to all newborn infants at risk of perinatal hepatitis B infections as soon as possible after birth.

Table 3: Summary of findings per outcome of timing of the first dose of recombinant DNA HBV vaccines

Outcome of interest	Timing of first dose		
	Birth dose (at ≤ 24 h) vs no birth dose	Birth dose at 0 to 3 days vs no birth dose	Birth dose given ≤ 2 weeks vs no birth dose
HBsAg seroprevalence	<p>Very low quality evidence</p> <p>One quasi-RCT³³ in a high endemicity region compared this schedule with a birth dose given < 24 h with schedules that did not include the birth dose; blood sampling was collected 3-6 months after immunization. The mothers of infants were HBsAg +, some of the included mothers were also HBeAg +. There was some evidence of lower seroprevalence rates in vaccine schedules without a birth dose, but this is based in a single study with high risk of bias.</p>	<p>Moderate quality evidence</p> <p>A cohort study³⁴ in children who received HBIG within 12 h of birth and 3 doses of vaccine at 0, 1, and 6 months reported that 2.3% of children were HBsAg +. Mothers were HBsAg +. Evidence suggests that a delay in the initial dose of vaccine was associated with an increased risk of carriage.</p> <p>One RCT³⁵ assessing plasma vaccine in a low endemicity area with blood sampling at 1-3 months after vaccination showed no evidence of a difference in seroprevalence rates between vaccine schedules. Mothers were HBsAg and HBeAg +, HBIG was used in addition to the vaccine.</p> <p>An observational study³⁴ in children receiving their first dose of hepatitis B at 1-3 days, 4-7 days, 8-61 and >62 days showed a strong relationship between time of first dose and chronic infection with a 3.3 OR (95%CI 1.3-8.2) for each unit increase in age.</p>	<p>There were no studies found that assessed this outcome</p>
Anti-HBs seroprotection	<p>Very low quality evidence</p> <p>Seven RCTs^{36 37 38 39 40 41 42 43} and two quasi-RCTs^{21 33} provide data on seroprotection rates. Six studies were in high endemicity areas, two were in a low, and one a moderate endemicity area. Mothers in one study³³ were HBsAg + (some were also HBeAg +); in the remaining studies mothers were either negative or their status was not reported. Meta-analysis was possible for three RCTs from high endemicity areas in which no difference in seroprotection rates was</p>	<p>Low quality evidence</p> <p>Two RCTs^{22 44 45 46} provided data on seroprotection rates comparing schedules with a birth dose given 0 to 3 days with no birth dose, with blood sampling at 1-3 months. One study^{45, 46} was in high endemicity area and another^{44, 45, 46} in low endemicity area. The mothers in one study were HBsAg + and some were also HBeAg +; in the other study mothers were negative or their status was not reported. Studies showed no difference in seroprotection</p>	<p>Very low quality evidence</p> <p>One RCT⁴⁷, one quasi-RCT⁴⁸ and one cohort study⁴⁹ provided data on seroprotection rates comparing four schedules with a birth dose given up to two weeks after birth with schedules that did not include a birth dose, with blood sampling at 1-3 months after immunization. The mothers in one study were HBsAg and HBeAg positive, and HBIG was used in addition to the vaccine; in the remaining studies the mothers were negative or their status was not reported. There was no</p>

Outcome of interest	Timing of first dose		
	Birth dose (at ≤ 24 h) vs no birth dose	Birth dose at 0 to 3 days vs no birth dose	Birth dose given ≤ 2 weeks vs no birth dose
GMCs of anti-HBs	<p>observed at 1-3 months after vaccination (RR 0.97 95%CI 0.95-0.98)</p> <p>There was no evidence of a difference in seroprotection rates between schedules except for one study which showed higher seroprotection (RR 1.12, 95% CI 1.01, 1.25) without a birth dose at 12-24 months post vaccinations.</p> <p>We are uncertain about the effect of birth dose versus no birth dose, because the evidence is of very low quality.</p>	<p>rates between vaccine schedules.</p>	<p>evidence of a difference in seroprotection rates between vaccine schedules for the RCT and quasi-RCT. A cohort study showed higher seroprotection rates without a birth dose (2, 3, 6 months vs. 0, 1, 3 months schedules; RR 1.27, 95% CI 1.07, 1.51).</p>
	<p>Low quality evidence Four RCTs^{36,37,38,40,39} and one quasi RCT²¹ provided data on GMCs comparing this schedule at 1-3 months post vaccination. Two studies were in high endemicity areas, two were in a low and one in a moderate endemicity area. None of the studies reported that mothers were HBsAg or HBeAg +.</p> <p>All studies found a higher antibody titres with a birth dose (<24 h) compared to schedules without a birth dose. For two studies from low endemicity areas the pooled GMC ratio was 0.49 (95% CI 0.37-0.66). One study²¹ from a moderate area found higher antibody titres with a birth dose schedule (GMC ratio 0.50 95%CI 0.36-0.70)</p> <p>We are uncertain of the effect of a birth dose compared to no birth dose schedule.</p>	<p>Moderate quality evidence One RCT²² in a high endemicity area were the mothers were all negative for HBsAg found higher antibody titres with a birth dose, at 1-3 months after vaccination. Birth dose given at 0 to 3 days of life probably leads to higher antibody concentrations.</p>	<p>Very low quality evidence One RCT⁴⁷ in a low endemicity region showed a WMD in log GMCs of -1.24 (95% CI -1.60 to -0.88). This corresponds to a GMC ratio of 0.30 (95% CI 0.20 to 0.41), which indicates that the birth dose schedule gave higher antibody concentrations 1-3 months post vaccination compared to the schedule without a birth dose. A quasi-RCT⁴⁸ reported data at 1-3 and 12-24 months after immunization, and results showed no difference in log GMCs for the compared schedules.</p>

Fig 3: Forest plot of difference in HBsAg seroprevalence between first dose of recombinant DNA HBV vaccine given within 24 h vs no birth dose

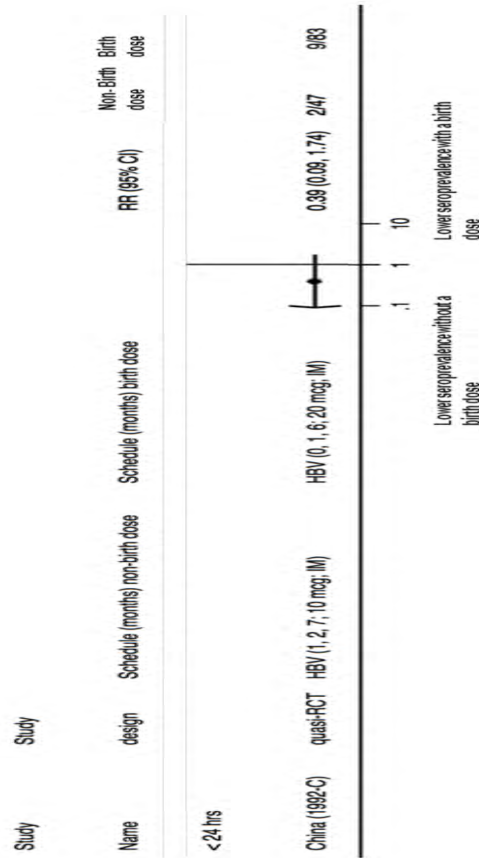
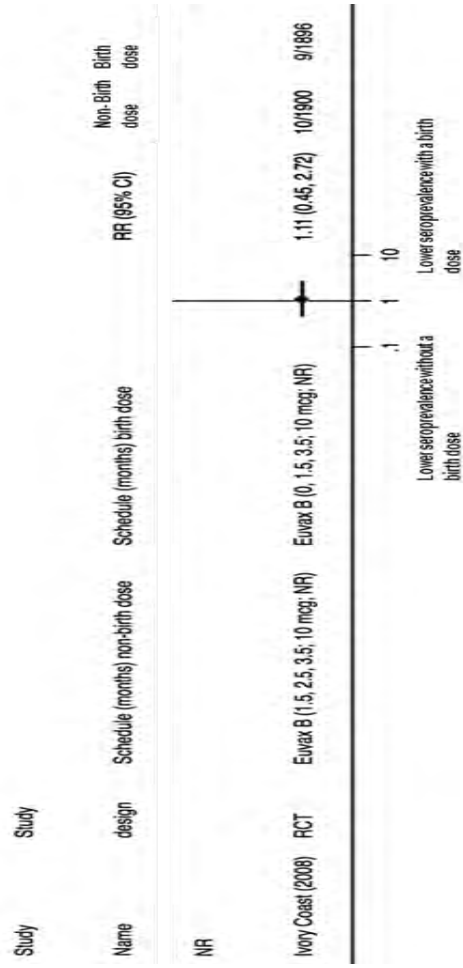


Fig 4: Forest Plot of difference in HBsAg seroprevalence between first dose of recombinant DNA HBV vaccine given in the first month of life vs no birth dose



Very limited evidence suggests lower seroprevalence rates in vaccine schedules without a birth dose compared to birth dose given < 24h.

Very limited evidence suggest no difference in seroprevalence rates between birth does given at “0 months”, exact timing not reported compared to no birth dose.

Forest plots for anti-HBs seroprotection and GMCs of anti-HBs available in the Targeted Update: Immunogenicity of recombinant DNA HBV vaccines: timing of first dose.

Effect of the interval between doses of recombinant DNA HBV vaccines on selected outcomes

There is no difference in rates of seroprotection with different intervals between doses in b0+2p and 3p dose schedules. For 2p schedules it is uncertain whether there is a difference as the available evidence is of very low quality.

There is no difference in antibody concentrations (GMCs) at 1-3 months post-vaccination and at longer follow up periods for b0+2p schedules. For 3p schedules, a 3,5,11 months vaccine schedule may result in higher antibody concentrations compared with a 2,4,6 months schedule, but the evidence is of low quality.⁸

Table 4: Summary of findings per outcome of interval between doses of recombinant DNA HBV vaccines

Outcome of interest	Interval between doses		
	Same schedules, different intervals (all ≥ 1 m) Birth dose + 2 p	Same schedules, different intervals (all ≥ 1 m) 3 p	Same schedules, different intervals (all ≥ 1 m) 2p
HBsAg seroprevalence	None of the included infants were HBsAg positive in serology performed 1-3 months after vaccination in both studies.	There were no studies found that assessed this outcome	There were no studies found that assessed this outcome
Anti-HBs seroprotection	Low quality evidence and very low quality evidence Three RCTs ^{50 51 52} and three quasi-RCTs ^{53 54} found no difference among comparisons, although our confidence in the findings is limited because of small samples and flaws in the conduct of included studies.	Very low quality evidence Two quasi-RCTs ^{56 48} and one cohort study ²⁴ conducted in low and moderate endemicity areas found no significant difference in seroprotection among the different vaccine schedules All studies reported vaccine intervals above one month.	Very low quality evidence A cohort study ²⁴ in low endemicity area found higher seroprotection rates in a 3,5 months vaccine schedule compared to 1, 3 months schedule.
GMCs of anti-HBs	Low quality evidence <i>Low endemicity</i> Two RCTs ^{57 51} conducted in low and in high endemicity areas found no difference in antibody concentrations in 0,1,6 months vaccination schedule compared to 0,1,2 months schedule at 12-24 months after vaccination.	Low quality evidence A single quasi-RCT ⁵⁶ provided data on GMCs comparing 3,5,11 months to a 2,4,6 months schedule. The 3, 5, 11 schedule gave higher antibody concentration at 1-3 months post vaccination	There were no studies found that assessed this outcome

Forest plots for anti-HBs seroprotection and GMCs of anti-HBs available in the Targeted Update: Immunogenicity of recombinant DNA HBV vaccines: same schedule, different intervals.

Effect of booster dose of Hepatitis B vaccine on selected outcomes

There is no evidence of a difference in seroprotection rates when a booster dose was given in both groups being compared. There is some evidence that 4p doses plus a booster gives higher antibody concentrations (GMCs) than 3p plus a booster. When a booster dose was compared with no booster dose, there is some evidence that a booster dose gives a higher proportion of seroprotection and higher levels of antibody concentrations (GMCs) at longer follow up periods of up to 15 years.⁸

Table 5: Summary of findings per outcome of booster of recombinant DNA HBV vaccines

Outcome of interest	Booster dose	
	3 primary doses + 1 booster (3p+1B) vs. 2 primary doses + 1 booster (2p+1B)	Booster vs no booster
HBsAg seroprevalence	There were no studies found that assessed this outcome.	There were no studies found that assessed this outcome
Anti-HBs seroprotection	<p>Low quality evidence Two cohort studies^{58 59 60} and one RCT^{61 62} conducted in low endemicity region found no evidence of a difference in seroprotection rates between schedules at pre-booster immunization. After booster immunization all three studies reported 100% anti-HBs seroprotection</p>	<p>Very low quality evidence 1 Cohort study^{14 17} and one RCT^{14 17} in Thailand (high endemicity), compared 4 primary doses plus 1 booster dose (4p+1B) vs. 4 primary doses without a booster dose (4p). After the booster vaccination, higher seroprotection was found for the 4p+1B schedule at 15 years.</p> <p>Low quality evidence A subset of a randomised trial^{14 17}, outcome measured at multiple time points compared 3 primary doses plus 1 booster dose (3p+1B) vs. 3 primary doses without a booster dose (3p). After booster immunization, higher seroprotection was found in the 3p+1B schedule at 24-36 months, 15 years and > 36 months.</p>

Outcome of interest	Booster dose	
	3 primary doses + 1 booster (3p+1B) vs. 2 primary doses + 1 booster (2p+1B)	Booster vs no booster
GMCs of anti-HBs	There were no studies found that assessed this outcome	<p>Very low quality evidence</p> <p>1 Cohort study^{14,17}, outcome measured at multiple time points; Comparison: 4 primary doses plus 1 booster dose (4p+1B) vs. 3 primary doses without a booster dose (3p). GMCs were higher for the group receiving a booster dose (4p+1B) at 12-24 months post booster. This effect was continued up to 15 years after the booster dose.</p> <p>Low quality evidence</p> <p>A subset of a randomised trial^{14,17}, outcome measured at multiple time points; Comparison: 3 primary doses plus 1 booster dose (3p+1B) vs. 3 primary doses without a booster dose (3p). After booster immunization, GMCs were significantly higher for the group receiving a booster dose (3p+1B). This effect was continued up to 15 years after the booster dose.</p>
	Forest plots for anti-HBs seroprotection and GMCs of anti-HBs available in the Targeted Update. Immunogenicity of recombinant DNA HBV vaccines: booster dose.	

A systematic review assessed the benefits and harms of a booster dose hepatitis B vaccination, more than five years after the primary vaccination, for preventing hepatitis B virus (HBV) infection in healthy individuals previously vaccinated with the hepatitis B vaccine, and with hepatitis B surface antibody levels (anti-HBs) below 10 mIU/mL.⁶³ and concluded that individuals adequately vaccinated in a 3-dose or 4- dose schedule do not require additional booster dose. Another systematic review⁶⁴ assessing the benefits and harms of booster dose hepatitis B vaccination, more than 5 years after primary vaccination for preventing HBV infection in healthy individuals previously vaccinated with the hepatitis B vaccine, and with hepatitis B surface antibody (anti-HBs) levels below 10mIU/ml. They found no eligible randomised clinical trials fulfilling the inclusion criteria for the review. A third review⁶⁵ examined literature and insights regarding the need for booster doses against hepatitis B published since 2002, starting from the article by Banatvala et al. Investigators concluded that there was no need for boosters in immunologically potent persons as long as a full course was adequately administered that respected the recommended timelines, as evidenced by studies conducted up to 20 years after the original immunization course.

Effect of catch up vaccination of Hepatitis B vaccine on selected outcomes

A systematic review assessed the benefits and harms of catch up vaccination of hepatitis B vaccines. There may be no difference in the proportion of children and adolescents becoming seroprotected 1-3 months post-vaccination when 2 primary catch-up doses are compared with 3 primary catch-up doses; these results remained consistent after a longer follow up period of 12 years.

There is some evidence indicating that catch-up vaccination schedules with 3 doses were associated with higher antibody concentrations (GMCs) at 1-3 months post-vaccination and at longer follow up periods, when compared with 2 primary catch-up doses. The clinical implications are unknown.

Results indicate there may be little or no difference in rates of serious adverse events when comparing 2 doses with 3 doses in children and adolescents.⁸

Table 6: Summary of findings per outcome of catch up vaccination of recombinant DNA HBV vaccines

Outcome of interest	Catch up vaccination	
	3 primary doses vs 2 primary doses	
HBsAg seroprevalence	<p>Low quality evidence One RCT⁶⁶ in a high endemicity region, compared three dose (0, 1, 6 months) versus two dose (0, 1 month) schedule. None of the participants were HBsAg positive in serology performed at 5, 12 and 22 years after vaccination.</p>	
	<p>Low quality evidence Nine RCTs^{58 59 61 67 68 69 70 71 72} with a higher dose of vaccine in the 2p schedule, apart from one comparison in Pakistan and two comparisons in USA. <i>1-3 months after last vaccination (Low, Moderate and High endemicity)</i> - Results from most studies suggest little or no difference in seroprotection among schedules <i>6-22 years follow-up (Low and High endemicity)</i>- Results from most studies suggest little or no difference in seroprotection among schedules.</p>	
Anti-HBs seroprotection	<p>Moderate quality evidence. Two RCTs^{59 61} from a low endemicity region found that a 0, 1, 6 months schedule gave higher antibody concentrations at 1-3 months post vaccination compared to the 0, 6 months schedule.</p>	
	<p>Low quality evidence One RCT⁷⁰ in a moderate endemicity region found that a 0, 1, 6 months schedule may lead to little or no difference in antibody concentrations at 1-3 months post vaccination compared to the 0, 6 months schedule.</p>	
	<p>Moderate quality evidence One RCT⁶⁸ in a high endemicity region found that a 0, 1, 6 months schedule probably leads to slightly higher antibody concentrations at 1-3 months post vaccination compared to the 0, 6 months schedule.</p>	
	<p>Low quality evidence One RCT⁵⁹ in children and adolescents in a low endemicity region found that a 0, 1, 6 months schedule probably may lead to little or no difference in antibody concentrations at 1-3 months post vaccination compared to the 0, 6 months schedule</p>	

Forest plots for anti-HBs seroprotection and GMCs of anti-HBs available in the Targeted Update: Immunogenicity of recombinant DNA HBV vaccines: catch-up vaccinations

Effect of birth dose of Hepatitis B vaccine started at different birth weights on selected outcomes

A systematic review assessed HBV vaccine effectiveness with different schedules in different populations. It covered studies published up to 2012. Only one clinical trial was included. It compared immunogenicity (at two weeks after final dose) from different schedules among LBW and normal weight babies. The main finding was that newborn with LBW would have better immunogenicity to HBV vaccine if the first dose is given at one month of age. Three observational studies included in the same review reached similar conclusions even after longer periods of follow up (up to three years).⁸

Table 7: Summary of findings per outcome of recombinant DNA HBV vaccines in low birth weight infants (1.0 to 2.0 kg) in Israel and China

Comparison: Recombinant DNA HBV vaccines started at 1.0 to 1.5 kg versus 2.0 kg

Outcome of interest	Plain language summary	Absolute effect		Relative effect (95% CI) N° of participants & studies	Certainty of the evidence (GRADE)
		Birth weight 1.0 to 1.5 kg	Birth weight 2.0 kg		
HBsAg seroprevalence	None of the included studies assessed this outcome.	Not measured	Not measured	2 Cohort studies, 196 participants	Not estimable
Anti-HBs seroprotection	It is uncertain whether delaying vaccination until a weight of 2.0 kg compared to early vaccination at 1.0 to 1.5 kg improves seroprotection, because the evidence is of very low quality.	Low endemicity			⊕⊕⊕⊕ VERY LOW ^{1,2}
		31/57 (54.39%)	37/40 (92.50%)	RR 0.59 (95% CI 0.46 to 0.76)	
		High endemicity		1 Cohort study, 97 participants	
GMCs of anti-HBs	It is uncertain whether delaying vaccination until a weight of 2.0 kg compared to early vaccination at 1.0 to 1.5 kg improves GMCs, because the evidence is of very low quality.	High endemicity			⊕⊕⊕⊕ VERY LOW ^{1,2}
		45/57 (78.95%)	38/42 (90.48%)	RR 0.87 (95% 0.74 to 1.03)	
		Low endemicity		1 Cohort study, 99 participants	
		Not reported	Not reported	GMCs measured by radioimmunoassay, GMC (IU/L) Mean (SD): <i>Birth weight 1.0 to 1.5 kg: 14.2 (SD not reported); N=57 participants</i> <i>Birth weight 2.0 kg: 119 (4.8); N=40 participants</i> 1 cohort study	
		High endemicity			

Outcome of interest	Plain language summary	Absolute effect		Relative effect (95% CI) N° of participants & studies	Certainty of the evidence (GRADE)
		Birth weight 1.0 to 1.5 kg	Birth weight 2.0 kg		
		Not reported	Not reported		
				GMTs measured by enzyme immunoassay, HBsAb: <i>Birth weight 1.0 to 1.5 kg:</i> 61, 95% CI 27 to 138; N=57 participants <i>Birth weight 2.0 kg:</i> 262, 95% CI 101 to 680; N=40 participants 1 Cohort study	

¹Downgraded one level for risk of bias: included studies were of high risk of bias

²Downgraded one level for imprecision: 95% CI includes null effect

Table 8: Summary of findings per outcome of recombinant DNA HBV vaccines in very low birth weight infants (≤ 1.5 kg) in the USA

Outcome of interest	Plain language summary	Absolute effect		Relative effect (95% CI)	Certainty of the evidence (GRADE)
		Birth weight ≤ 1.0 kg	Birth weight 1.5 kg		
Anti-HBs seroprotection	It is uncertain whether starting vaccination at 1.5 kg compared to starting at ≤ 1.0 kg improves seroprotection, because the evidence is of very low quality.	17/22 (77.27%)	24/28 (85.71%)	RR 0.92 (0.70 to 1.20) Non-randomised data from 1 RCT, 50 participants	$\oplus\oplus\oplus\oplus$ VERY LOW ^{1,2}

¹Downgraded one level for risk of bias: included studies were of high risk of bias

²Downgraded one level for imprecision: 95% CI includes null effect

Forest plots for anti-HBs seroprotection available in the Targeted Update: Immunogenicity of recombinant DNA HBV vaccines: timing of first dose.

Evidence shows the reduced immunogenicity of vaccination in low birth weight infants. However delaying vaccination would leave the babies at risk. It is therefore recommended that all babies should have a birth dose whatever their birth weight and those with a low birth weight should start their primary schedule of vaccination 1 month later.

HIV infected population:

A systematic review and meta-analysis assessed the long term immune response of vaccines in HIV infected children and adults.⁷³ The review included observational and experimental studies addressing persistence of antibodies for more than 6 months after the last dose. Twelve studies on hepatitis B were available with follow up times from 15 to 112 months, 6 of them in adults. As observed in figure 5 there is no clear difference in seroprotection length between vaccines with different titres composition. After 3 doses of HBV containing 40 ug of antigen, 71% of primary responders have seroprotective level titers one year after vaccination, 33% to 61% after year 2, and 40% after year 5. Despite the slightly higher titer in the 40 ugrs group, over time titres become comparable to those receiving a HBV with 20 ugrs. Therefore, administering a higher titre HBV to this group does not seem to improve maintenance of seroprotection compared to standard doses (41% vs 50% respectively). Figures 6 and 7.

Figure 5. Percent of individuals with protective levels of Anti HBs in relation to time elapsed since last dose

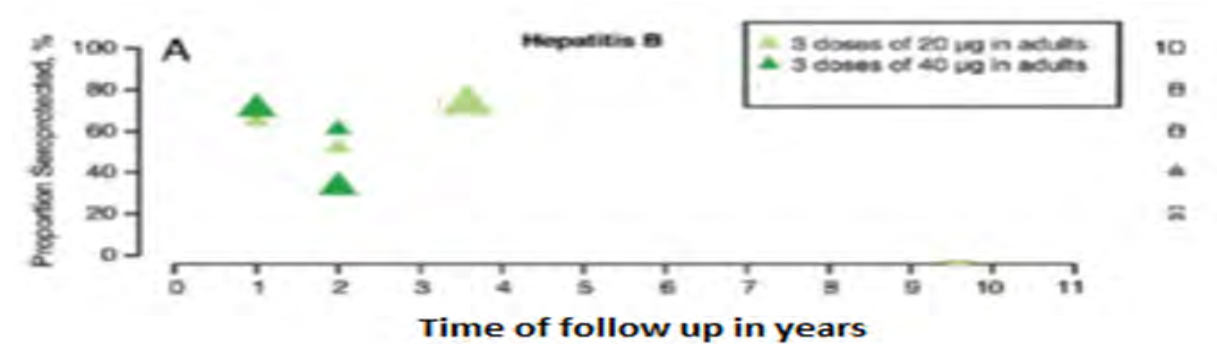


Figure 6: Predicted proportion of adults with protective antibodies after 2 years follow up

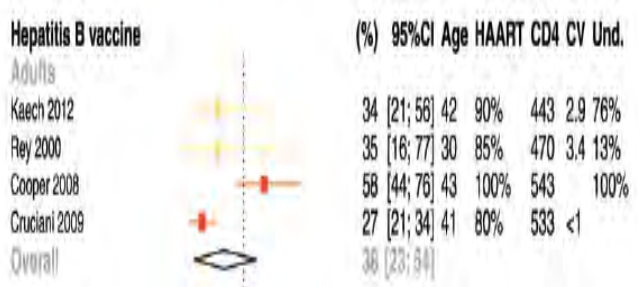


Figure 7: Predicted proportion of adults with protective antibodies after 5 years follow up.



A Cochrane review⁷⁴ evaluated the impact of HBV vaccination on prevention of morbidity and mortality in HIV positive patients and included only clinical trials. Only one RCT was found. It described HBV vaccination in 26 participants with HIV infection followed for 3 years on a monthly basis. Most participants lost immunity when ART was stopped. They were unable to test whether HBV vaccine was better than placebo to prevent HBV infection and complications. Therefore the evidence is insufficient to support any recommendation on HBV vaccination use for HIV persons.

Another systematic review⁷⁵, found several small clinical trials assessing the effectiveness of Hepatitis B vaccine among HIV infected people. They used different vaccination schemes, sites of administration, vaccine adjuvants, HBsAg dose, or number of injections. The outcome in all of them was immunogenicity since most followed patients for less than 12 months. The main conclusion was that HIV infected adults vaccinated with three or four doses using double amount of antigen (40 ug) had a higher peak of antibodies. However, follow up was limited to 6 to 12 months after the last dose. One of the trials with the highest quality, double blind RCT, did not found differences between standard doses and double doses.

In conclusion, there is no strong evidence to change current WHO recommendation on vaccination of HIV positive population at any age. Recommending periodical monitoring of anti HBs titres may be discussed at SAGE.

Long term protection

A meta-analysis⁷⁶ assessed the long-term immunity induced by HB vaccines and the possible need of a booster dose. The results from this meta-analysis show that protection provided by HB vaccine persists for at least two decades in the great majority of immunocompetent adequately vaccinated individuals. Three doses of HB vaccine ensure a good protection against infection for up to 20 years. However, additional longer-term studies should be conducted to explore vaccine efficacy and the need of booster doses in different subgroups of the population.

Vaccination of Health Care Workers

Hepatitis B virus (HBV) infection is a well-recognized occupational risk for health-care workers (HCW) and HCW trainees with blood and body fluid exposures.⁷⁷ Because of their contact with patients or infective material from patients, susceptible health-care workers (HCW) are at considerably greater risk for exposure to and transmission of HBV than the adult population as a whole.^(77 78) The risk for HBV infection is greatest among HCW with exposures to blood or body fluids from patients who are hepatitis B e antigen (HBeAg) positive, a marker of high HBV replication and viral load.⁽⁷⁹⁾ HBV is stable, remaining infectious on environmental surfaces for at least 7 days, and is transmissible in the absence of visible blood.^(80, 81) HCW do not recognize all exposures to potentially infectious blood and body fluids, or contaminated environments.^(82, 83, 84 85 86 87) Even if exposures are recognized, HCW often do not seek post-exposure prophylactic management.⁽⁸⁸⁾ Optimal use of hepatitis B vaccine safeguards the health of workers and provides greater protection for patients from becoming infected through exposure to infected workers or contaminated environments.⁸⁹

Does the available evidence support flexibility in the requirement for cold chain storage of Hepatitis B monovalent vaccines in order to expand the delivery of the birth dose?

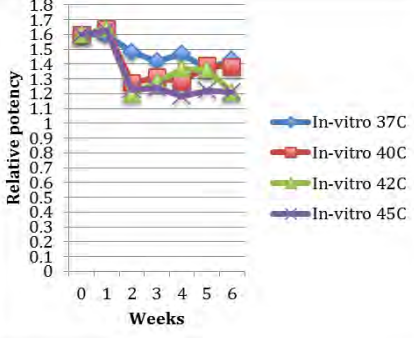
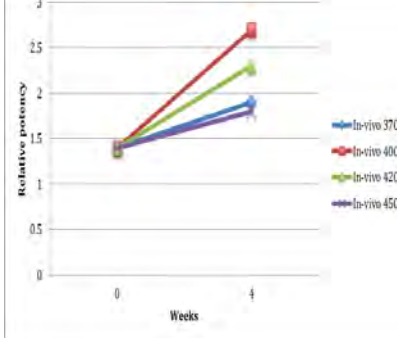
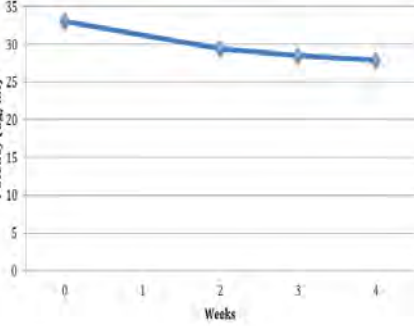
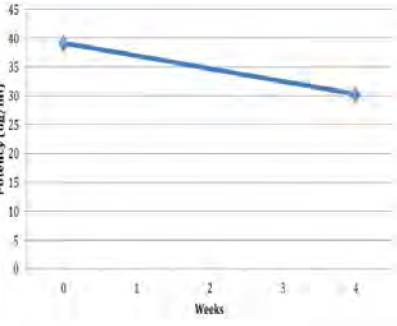
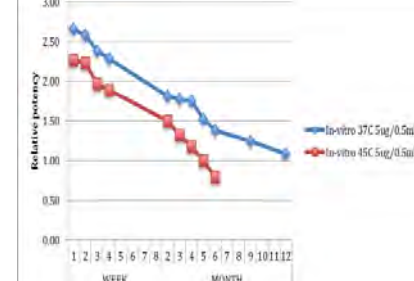
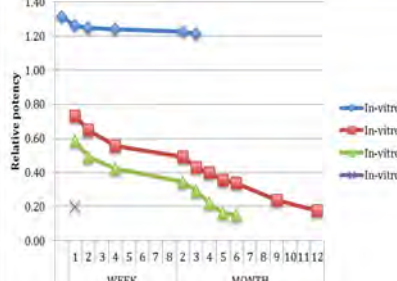
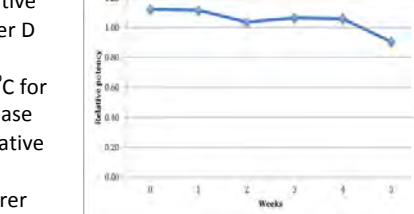
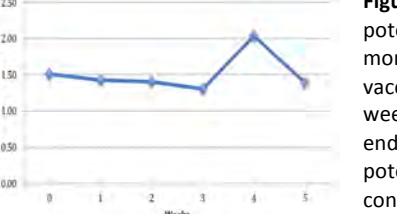
Thermostability of hepatitis B vaccines

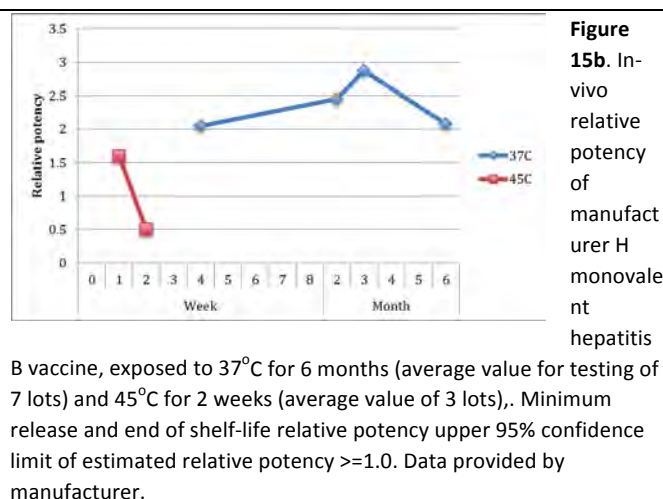
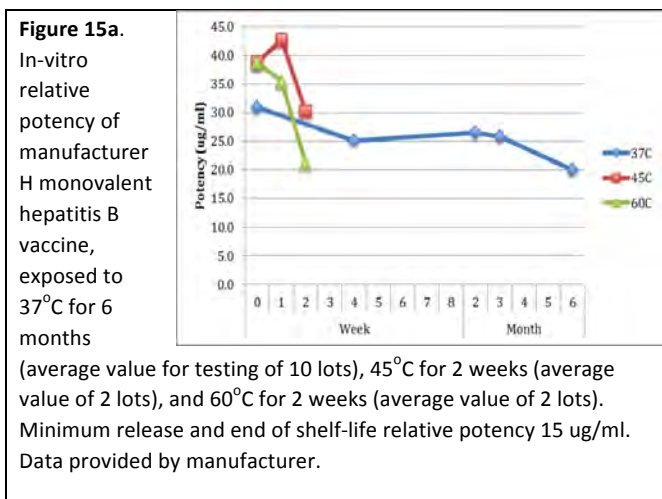
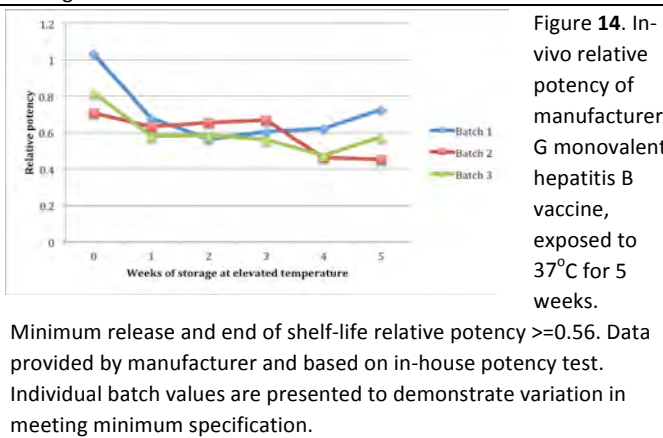
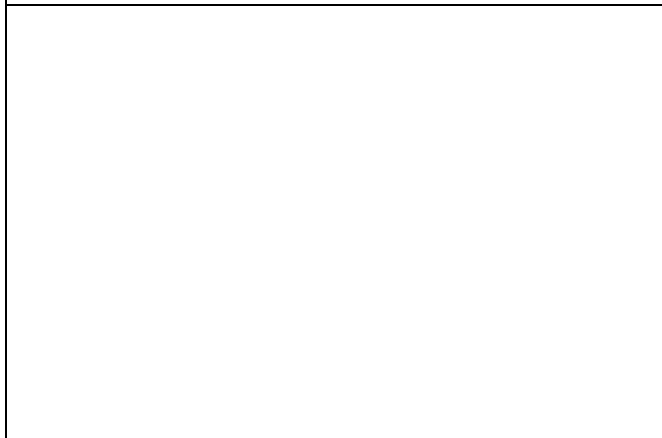
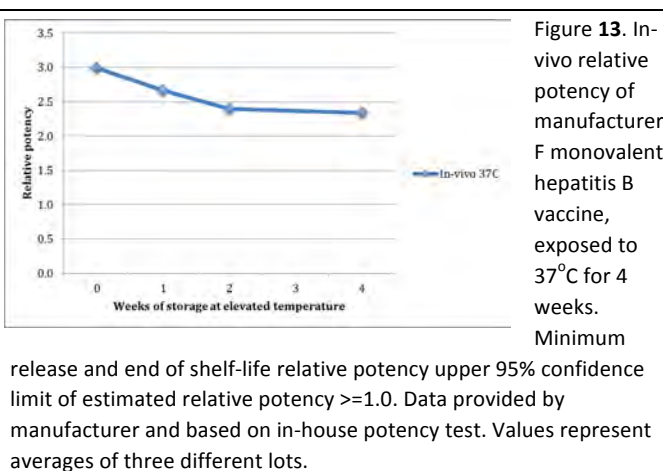
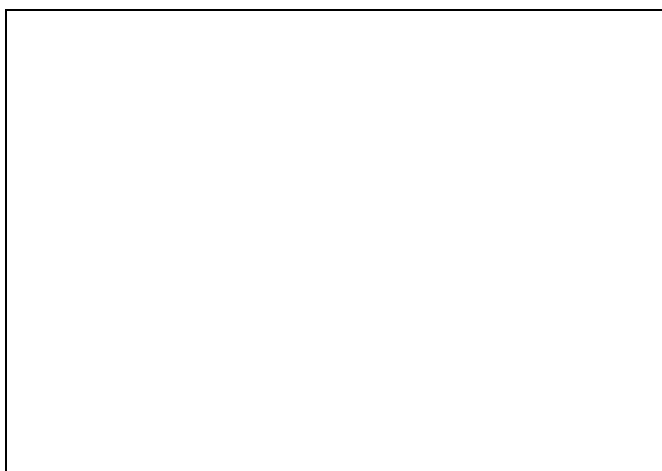
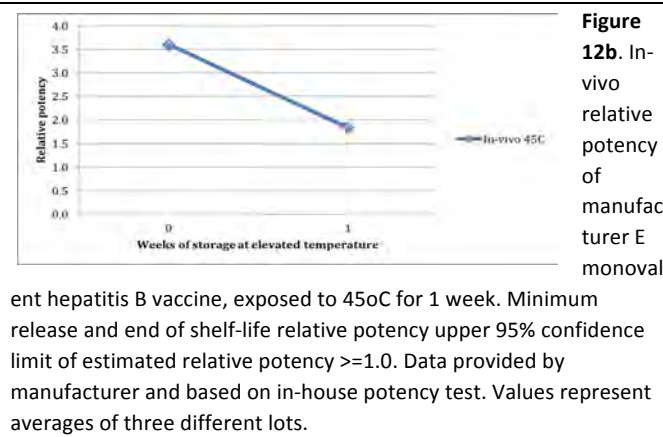
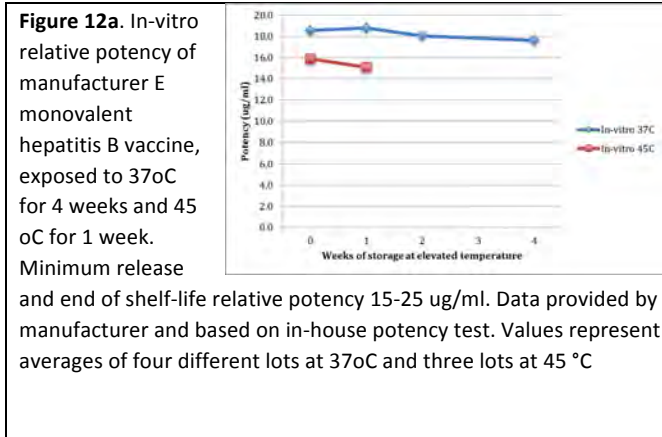
Introduction: In many resource-poor countries, a substantial percentage of births may occur outside of health care facilities. Lack of access to vaccine in cold storage may reduce birth-dose hepatitis B vaccine (HBV) coverage and thus place infants at risk of perinatal transmission. One mechanism to address this issue would be to allow vaccine to be out of the cold chain at the point of delivery, but few manufacturers have pursued an on-label indication for storage at >8°C (known as the extended controlled temperature chain [ECTC]), including the World Health Organization (WHO) CTC programmatic approach allowing for vaccine to be stored at 40°C for three days.

Methods: Thermostability data was obtained from eight of nine monovalent WHO prequalified HBV manufacturers. A systematic literature review was conducted to identify studies in which HBV was stored outside the cold chain.

Results: Eight manufacturers provided in-vitro potency results following storage at 37°C for four weeks, and all met minimum lot release specifications, with an average decrease in potency of 16%. Four manufacturers assessed in-vitro potency after 1 to 4 weeks storage at 45°C, and five assessed in-vivo potency after storage at 37-45°C and all met minimum specifications as well. The systematic literature review identified four controlled field studies that evaluated an out-of-the-cold-chain approach; no differences were seen in GMTs or seroconversion between children who received vaccine in intervention versus non-intervention communities. Similarly, two experimental studies in humans and three in animals supported HBV thermostability over a four-week period.

Conclusions: Since an important proportion of deliveries at home or limited cold chain in peripheral health facilities may hamper access to the birth dose, a review of published data and manufacturers' data assessed the thermostability of Hepatitis B monovalent vaccine. Existing data indicates that most hepatitis B vaccines are heat stable and have been found to maintain immunogenicity after exposure to temperatures of up to +45°C for one week and temperatures up to +37°C and +41°C for several weeks. Field experience suggest there maybe programmatic advantages in keeping hepatitis B vaccine in ambient temperatures at service delivery points, especially as a strategy for reaching home births.

<p>Figure 8a In-vitro relative potency of manufacturer A monovalent hepatitis B vaccine, exposed to different temperatures for different time periods. Minimum release and end of shelf-life relative potency ≥ 0.45. Data provided by manufacturer and results based on Murex test kit (Diasorin).</p>	 <p>Relative potency</p> <p>Weeks</p> <p>In-vitro 37C In-vitro 40C In-vitro 42C In-vitro 45C</p>	<p>Figure 8b. In-vivo relative potency of manufacturer A monovalent hepatitis B vaccine, exposed to different temperatures for different time periods. Minimum release and end of shelf-life relative potency upper 95% confidence limit of estimated relative potency ≥ 1.0. Data provided by manufacturer.</p>	 <p>Relative potency</p> <p>Weeks</p> <p>In-vivo 37C In-vivo 40C In-vivo 42C In-vivo 45C</p>
<p>Figure 9a. In-vitro relative potency of manufacturer B monovalent hepatitis B vaccine, exposed to 37°C for 4 weeks. Minimum release and end of shelf-life relative potency not specified but manufacturer indicated data confirmed stability to 4 weeks. Data provided by manufacturer and based on in-house potency test. Values represent averages of two different lots.</p>	 <p>Potency (ug/ml)</p> <p>Weeks</p>	<p>Figure 9b. In-vivo relative potency of manufacturer B monovalent hepatitis B vaccine, exposed to 37°C for 4 weeks. Minimum release and end of shelf-life relative potency not specified but manufacturer indicated data confirmed stability to 4 weeks. Data provided by manufacturer and based on in-house potency test. Values represent averages of two different lots.</p>	 <p>Potency (ug/ml)</p> <p>Weeks</p>
<p>Figure 10a. Study 1: in-vitro relative potency of manufacturer C monovalent hepatitis B vaccine, exposed to different temperatures for different time periods. Minimum release and end of shelf-life relative potency ≥ 0.50. Data provided by manufacturer. Values represent averages of two different lots.</p>	 <p>Relative potency</p> <p>WEEK MONTH</p> <p>In-vitro 37C 5ug/0.5ml In-vitro 45C 5ug/0.5ml</p>	<p>Figure 10b. Study 2: in-vitro relative potency of manufacturer C monovalent hepatitis B vaccine, exposed to different temperatures for different time periods. Minimum release and end of shelf-life relative potency ≥ 0.50. Data provided by manufacturer. Values represent averages of three different lots.</p>	 <p>Relative potency</p> <p>WEEK MONTH</p> <p>In-vitro 4C 5ug/0.5ml In-vitro 37C 5ug/0.5ml In-vitro 45C 5ug/0.5ml In-vitro 70C 5ug/0.5ml</p>
<p>Figure 11a. In-vitro relative potency of manufacturer D monovalent hepatitis B vaccine, exposed to 37°C for 5 weeks. Minimum release and end of shelf-life relative potency ≥ 0.80. Data provided by manufacturer and based on in-house potency test. Values represent averages of three different lots.</p>	 <p>Relative potency</p> <p>Weeks</p>	<p>Figure 11b. In-vivo relative potency of manufacturer D monovalent hepatitis B vaccine, exposed to 37°C for 5 weeks. Minimum release and end of shelf-life relative potency upper 95% confidence limit of estimated relative potency ≥ 1.0. Data provided by manufacturer and based on in-house potency test. Values represent averages of three different lots.</p>	 <p>Relative potency</p> <p>Weeks</p>



Barriers to introduce the Hepatitis B birth dose. Ensuring that all infants receive a dose of hepatitis B vaccine within 24 hours of birth requires implementation of specific programmatic measures. Increasing the number of infants born in facilities or attended by trained health staff would improve birth dose coverage. Ensuring that there is coordination between immunization services and maternal health services is important so that vaccine is available at the place of delivery or immediately after birth. Expanding vaccine management systems and innovative outreach to provide vaccine for home births⁹⁰ will ensure that hepatitis vaccine is available in settings where births take place. Efforts to develop new heat-stable and freeze-stable hepatitis B vaccine will aid these attempts. In addition, health promotion efforts aimed at parents and training aimed at providers are needed to increase awareness about the importance of administering hepatitis B vaccine within 24 hours of birth.⁹¹ A large list of potential barriers for birth dose delivery was found. Barriers arising from health services in developing countries included: low coverage of institutional birth, poor performance of outreach vaccination activities, logistical constriction for cold chain in rural and remote areas, out of pocket costs, and false contraindications. Potential barriers from health care users included most frequently: concerns about health effects, false contraindications, married category of mothers and mother's education. In developed countries barriers included confusion about reimbursement procedures and immigration status of mothers. No specific study for barriers impairing hepatitis B birth dose delivery was found in the Eastern Mediterranean region. New ways to deliver hepatitis B vaccines to neonates being born at home should be envisaged if the goal of eliminating perinatal transmission of hepatitis B is to be achieved.

Table 9. Barriers for timely hepatitis B birth dose in Western Pacific Region Community based studies

Author	Year published	Country	Study setting	Population studied	Reasons 1	Reasons 2	Reasons 3	Reason 4	Reason 5
Mao	2013	Cambodia	Community	General	Maternal education	Birth at home			
Cui	2006	China	Community	General	Birth at home				
Zhou	2009	China	Community	General	Birth at home	Parent awareness on HBV	Ethnic minority	Parents concern on adverse effect	
Patel	2014	Philippines	Community	General	Birth at home				
Murakami	2008	Vietnam	Community	General	Vaccine storage	Pregnancy tracking performance	Conflicting guidelines at hospitals	Private maternity services	Low birth weight
Murakami	2014	Vietnam	Community	General	Media report on adverse effects				

Table 10. Barriers for timely hepatitis B birth dose in Western Pacific Region. Hospital based studies

Author	Year published	Country	Population studied	Reasons 1	Reasons 2	Reasons 3	Reason 4	Reason 5	Reason 6
Sahhar	2015	Australia	high risk	Care by obstetrician					
Kang	2014	China	high risk	Low birth weight	Prematurity				
Keuatvongsa	2013	Laos	General	Vaccine outage	False contraindications	Health workers training	Limited outreach services		
Wiesen	2016	New Guinea	General	Health workers training/supervision	Quality of outreach services	HB vacc available in facility	Vaccination in weekends	Birth at home	Mother knowledge of HBV
Patel	2014	Philippines	General	Out of pocket Cost	False contraindications	HW training	Vaccine availability	Private providers	Birth at home
Sobel	2011	Philippines	General	Trained staff	Standing order for HB admon	Copy of HB vacc policy in health facility			

Table 11. Barriers for hepatitis B birth dose in AMRO Region

Author	Year published	Country	Study setting	Population studied	Reasons 1	Reasons 2	Reasons 3	Reason 4	Reason 5
Bascom	2007	Puerto Rico	Hospital	General	Month of delivery	Birth weight			
Dayan	2001	USA	Hospital	high risk	Mother age	Hospital Outreach inconvenience	Being less educated	Being single	
Aiken	2001	USA	Hospital	Managers	Reimbursement				
Thomas	2002	USA	Hospital	high risk	Thimerosal				
Cabana	2002	USA	Hospital	Managers	Thimerosal				
Clark	2004	USA	Hospital	Managers	Thimerosal				
Cooper	2005	USA	Hospital	HW	Tracking hospital immunizations	High cost	reimbursing	parents unwilling	Safety concerns
Zhao	2011	USA	Community	General	2 or + providers	Public/private provider	Mother Married status	Mother education	
Myers	2015	USA	Hospital	General	Marital status	Race			

Table 12. Barriers for hepatitis B birth dose in EURO Region

Author	Year published	Country	Study setting	Population studied	Reasons 1	Reasons 2	Reasons 3
Sloan	2005	UK	Hospital	high risk	Year of birth	antenatal booking	Maternal serological status
Giraudon	2009	UK	Hospital	high risk	London sector of residence	Command of english	

Table 13. Barriers for hepatitis B birth dose in SEARO Region

Author	Year publish	Country	Study setting	Population studied	Reasons 1	Reason 2	Reason 3	Reason 4	Reason 5
Alexander	2013	India	Hospital	high risk	Birth outside				
Lahariya	2013	India	Community	General	Fear of vaccine wastage	HW poor knowledge			
Creati	2007	Indonesia	Community	General	policy weakness	limited transport	poor communication	cold chain	HW training

Social and demographic factors related to timely birth dose in The Gambia are described by Miyahara for The Gambia. Living in rural areas was the most important risk factor for no receiving a birth dose (OR=6,1 CI 3.2-11.8).

In addition, information provided by the African Regional Office and the South-East Regional Office provides further insight on the countries progress and expressed barriers to the introduction of the Hepatitis B vaccine birth dose. Data on the following questions was collected:

1. Have the NITAG's recommended the introduction of the hepatitis B vaccine birth dose
2. What are the main barriers to the introduction of the birth dose?
3. What are the recommendations to overcome these barriers?

According to the information provided by the AFRO region, 10 of 47 countries have introduced the hepatitis B birth dose in their immunization schedule. Among the nine countries that provided HepB-BD in their vaccination schedule in 2015, coverage was <80% in three (Angola at 19%, Mauritania at 51% and Nigeria at 43%), between 80-95% in four (Botswana and Namibia at 87%, Cap Vert at 93% and Sao Tome at 91%), and >95% in two (Algeria and The Gambia). In Sierra Leone, the EPI Technical Committee (TCC) has recommended the introduction of Hepatitis B birth dose for 2018. Niger is planning to introduce the birth dose in 2019. In Mauritius the hepatitis B birth dose is given to babies whose mothers are HBV infected. The number of life births estimated for the AFRO region in 2015 was 35 380 279⁹². The number of life births in the countries that have no yet introduced the birth dose was 26 966 573 in 2015⁹². The proportion of life births taking place in homes ranges from 8% in the Congo to 89% in Ethiopia.⁹³ Data from the World Bank shows that the range of births attended by skilled health staff in AFRO is 15.5% in Ethiopia to 99.2% in Mauritius.⁹⁴ Among the 37 countries that have not yet introduced the birth dose, 10 had an established NITAG and three had recommended the birth dose introduction into the national schedules. One country, Cameroon is pending approval of the 2017 budget to purchase the birth dose.

The most common mentioned barriers in the AFRO region to introduce the birth dose are the lack of funding for the birth dose programmes, the percentage of births that take place outside health facilities, the insufficient disease burden data, the vaccine storage facilities and access to cold chain and the central policies and guidelines.

Currently 7 of 11 countries in the SEAR have the hepatitis B birth dose in their national schedule; one country introduced it in February 2016. Among the six countries that provided HepB-BD in their vaccination schedule in 2015, coverage was <80% in two (Bhutan at 78% and India at 44%), between 80-95% in one (Indonesia), and >95% in three (DPRK, Maldives, and Thailand). Bangladesh, Myanmar, Sri Lanka, and Nepal do not provide a HepB-BD, though both Myanmar and Nepal may reconsider full or partial introduction of the birth dose as part of their national control strategies. Indonesia is using Uniject outside of cold chain and Timor Leste will do so for home deliveries or in places far from health centers. The barriers for introduction of the birth dose are the lack of funds, as there is no Gavi support for the birth dose, insufficient disease burden data, the use of out of the cold chain (OCC) and/or future

controlled temperature chain (CTC). The actions points suggested to overcome these barriers were advocacy for government budget allocation, conduct seroprevalence surveys, conduct country pilot studies on the use of the OCC and contribute to the capacity building of NITAGs and national regulatory authorities (NRAs). The SEAR region also provided information on the barriers to achieving high coverage. Those included the number of home deliveries without skilled birth attendance, the lack of awareness and/or training among health staff at birthing facilities (incomplete integration in newborn care packages, false contraindications, fear of adverse events following immunization (AEFI), weak coordination between MCH and EPI), challenges in the vaccine supply (presentation and availability, access, management like open vial policy), incomplete participation of the private sector.

Economic Evaluation of Hepatitis B vaccination

Economic evaluations of *Hepatitis B* vaccine: systematic review of the literature⁹⁵

The objective was to systematically review the evidence for economic evaluations of HBV vaccination in LMICs.

Key findings included: (1) Since the introduction of HBV only 19 CEA studies in LMICs have been identified; (2) HBV vaccination in LMICs has favorable cost-effective results in almost all published studies using per GDP per capita cost-effectiveness thresholds; (3) This systematic review highlights that vaccine price, prevalence of HBV, discount rate, cost component, wastage rate of vaccine, and vaccine efficacy are the key drivers and play influential role in the decision to implement HBV immunization program in LMIC and; (4) In addition to cost-effectiveness results, decision makers should consider feasibility, affordability and sustainability of vaccination programs to ensure equitable access of vaccine when deciding whether to include HBV vaccination in national immunization program.

Out of 19 studies, 18 studies considered HBV vaccination cost-saving or cost-effective intervention, while only one study showed that it was unlikely to be cost-effective . All six studies investigating birth dose HBV vaccination showed that it was cost-effective.

Most studies conducted one-way sensitivity analysis. Probabilistic sensitivity analysis (PSA) was conducted in eight studies. The most reported influential parameters were prevalence of HBV (7 of 19 studies), vaccine price (7 of 19 studies), discount rate (6 of 19 studies), cost component (4 of 19 studies), wastage rate of vaccine (3 of 19 studies), and vaccine coverage (2 of 19 studies).

In conclusion studies are overwhelmingly favourable with the exception of one study in India which did not find a birth dose cost effective. There was a paucity of studies and none of them used transmission models and modern methods. New studies would be valuable, particularly to NITAGs tasked with developing national policies.

For further information refer to the document: Hepatitis B Vaccination: An Updated Systematic Review of Economic Evaluations in Low and Middle Income Countries.

Table 14: Economics evaluation of Hepatitis B vaccination in LMICs

Study	Country	Type of economic analysis	Model	Perspective	Sponsor	Immunization approach*	Effectiveness measure	Threshold
Hall, 1993	The Gambia	CEA	None	Society	Department for Co-operation and Development of the Ministry of Foreign Affairs of Italy. The vaccine for the study was donated by Merck, Sharp, and Dohme.	Universal	Death averted	US\$2750 (year 1979)
Liu, 1995	China	CBA	Static model: Decision tree	Society	N/A	Universal	BCR	N/A
Edmunds, 2000	Ethiopia	CEA, CMA	None	Healthcare	University of Warwick's Research and Training Development Fund. Wellcome Health Services Research Fellowship.	N/A	Per fully vaccinated child	N/A
Hu, 2001	China	CUA	Static model: Decision tree	Society	N/A	Targeted*	DALY	N/A
Aggarwal, 2003	India	CUA	Static model: Markov	Society	N/A	Universal	LYG, QALY	GNP per capita (US\$440 for year 1999)
Prakash, 2003	India	CUA	Static model: Decision tree	Society	N/A	Universal	DALY	N/A
Adibi, 2004	Iran	CEA	Static model: Decision tree	Society and Healthcare	Research Center for Gastroenterology and Liver Disease, Shaheed Beheshti University of Medical Sciences, Tehran, Iran	Targeted*	Per chronic infection prevented	GDP per capita (US\$1641 for year 2002)
Sahni, 2004	India	CBA, CUA	Static model: -	Society	The Canadian International Development Authority (CIDA)	Universal	QALY	GNP per capita (US\$466 for year 2001)
Griffiths, 2005	Mozambique	CUA	Static model: -	Society	N/A	Universal	QALY	GNP per capita (US\$210 for year 2001)
Vimolket, 2005	Thailand	CEA	Static model: Decision tree	Society	The Center of Excellence Research Fund, Chulalongkorn University; and the Thailand Research Fund, Senior Research Scholar.	Universal	Per case averted	N/A
Kim, 2007	The Gambia	CUA	Static model: -	Society and Healthcare	Supported in part by a Harvard Graduate Society Fellowship.	Universal	DALY	GDP per capita (US\$300 for year 2002)
Hutton, 2010	China	CEA	Probability tree and Markov	Societal	N/A	Catch-up program	Death, HBV infections averted, and QALYs	GDP per capita (US\$2,500 for year 2008)
Guo, 2012	China	CEA HBIG	N/A	N/A	The National Nature Science Foundation of China	N/A	DALY averted	N/A
Klingler, 2012	Mozambique	CEA	Markov	Payer	N/A		DALY averted	GDP per capita (US\$441 for year 2008)
Tu, 2012	Vietnam	CEA	Decision tree and Markov	Societal, healthcare, and payer	The Dutch Higher Education Foundation (NUFFIC)	Universal	LYG and QALY	GDP per capita (US\$440 for year 2002)

Study	Country	Type of economic analysis	Model	Perspective	Sponsor	Immunization approach *	Effectiveness measure	Threshold
Lu, 2013	China	CEA, CUA	Decision tree and Markov	Societal and healthcare payer	N/A	Universal	New infections, HCC, deaths, LYG, and QLAY	GDP per capita (US\$1,136 for year 2002)
Jia, 2014	China	CEA	Decision tree and Markov	Societal	National Health and Family Planning Commission and Minister of Science and Technology	Catch-up program	QLAY	GDP per capita (US\$5,414 for year 2013)
Zheng, 2015	China	CBA	Decision tree	Direct and Societal	The Chinese Ministry of Science and Technology Program for Important Infectious Diseases Control and Prevention	Screening based vaccination for 21-59 years old	NPV, BCR	BCR ≥ 1
Chen, 2016	China	CBA	Decision tree and Markov	Direct and Societal	The Chinese Ministry of Science and Technology Program for Important Infectious Diseases Control and Prevention	Combine with one dose of HBIG for infants with HBsAg +ve mothers	NPV, BCR	BCR ≥ 1

* Universal = Immunization given to the whole general population or to all within a certain age group of the population (newborns, adolescents, adults, and so on), Targeted and catch-up = Immunization programs selectively targeting individuals at risk of hepatitis B virus

BCR: Benefit cost ratio; CBA: Cost-benefit analysis; CEA: Cost-effectiveness analysis; CMA: Cost-minimization analysis; CUA: Cost-utility analysis; DALY: Disability-adjusted life year; GNP: Gross national product; GDP: Gross domestic product; HBIG: Hepatitis B immunoglobulin; HCC: Hepatocellular carcinoma; QALY: Quality-adjusted life year; LYG: Life year gained; N/A: Not applicable; NPV: Net present value.

Table 15: Vaccine coverage, efficacy duration, price, discounting, and results

Study	Vaccine coverage	Vaccine efficacy /protection duration	Vaccine price per dose (US\$)*		Discounting rate (%)		Results (US\$, at costing year)
			Price	Costing year	Cost	Effect	
Hall, 1993	10%-15%	99% (95%CI 91-100)	3	1998	6	N/S	Cost-effective US\$150-200 per death averted
Liu, 1995	100%	50% (HBsAg+ by 3 doses of 10µg) 90% (HBsAg+ by 3 doses of 30µg) 90% (HBsAg-)	6.53 (for 3 doses of 10µg) 12.37 (for 3 doses of 30µg)	1990	-	-	Cost saving With screening 30µg X3 for HBsAg+ and 10µg X3 for HBsAg-: BCR = 42.41 30µg X3 for HBsAg+ and no vaccination for HBsAg-: BCR = 48.01 Without screening 10µg X3 for both HBsAg+ and HBsAg-: BCR = 43.64
Edmunds, 2000	60%	N/A	0.35-1.69	1996	6	N/S	Cost-effective US\$7.83 per fully vaccinated child (Extrapolate the cost-effectiveness in terms of outcome measure such as life years gained relative to The Gambia)
Hu, 2001	100%	90%	2.97	2001	3	-	Cost-effective Without screening: CER = 392.7 With screening: CER = 251.9
Aggarwal, 2003	75% (40% - 95%)	95%	3	2002	3	0	Cost-effective US\$16.27/LYG and US\$13.22/QALY
Prakash, 2003	52%	95%	0.75	1993	3	0 or 3	Cost-effective

Study	Vaccine coverage	Vaccine efficacy /protection duration	Vaccine price per dose (US\$)*		Discounting rate (%)		Results (US\$, at costing year)
			Price	Costing year	Cost	Effect	
Adibi, 2004	100%	N/A	4.8	2003	3	0	US\$27.36/DALY Cost-effective US\$202 per chronic infection prevented (no HBcAb screening) US\$197 per chronic infection prevented (with HBcAb screening)
Sahni, 2004	N/A	100%	4.2	2001	3	0	Not cost-effective US\$2909/QALY (US\$8894/ discounted QALY)
Griffiths, 2005	80% (70% - 85%)	95% (90% - 99%)	0.27 for monovalent vaccine and 1.2 for DTP-Hepatitis B	2001	3	0 or 5	Cost-effective Undiscounted US\$436 per death averted, US\$15/DALY (monovalent), and US\$36/DALY (combination vaccine) Discounted US\$1833 per death averted, US\$19/DALY (monovalent), and US\$47/DALY (combination vaccine)
Vimolket, 2005	N/A	N/A	3.75	2004	N/S	N/S	Cost-effective US\$2201 per case averted (screen for HBsAg, then vaccination) US\$464 per case averted (screen for HBsAg, HBeAg, then vaccination) US\$152 per case averted (universal vaccination) (Based on funds presently available in Thailand, universal vaccination should certainly be continued)
Kim, 2007	94% (85% - 100%)	95% (90% - 100%)	0.32	2002	3	3	Cost-effective US\$28/DALY (societal perspective) US\$47/DALY (healthcare perspective)
Hulton, 2010	100% (catch up for those who missed newborn vaccination)	95%	0.34	2008	3	3	Cost-saving
Guo, 2012	N/A	N/A	30.93, HBIG	N/A	N/A	N/A	Cost-effective US\$118.61/DALY averted
Klingler, 2012	55%	88%	0.71	2008	3	3	Cost-effective US\$250.95/DALY averted
Tu, 2012	70%	84%	1	2008	0 or 3	0 or N/S	Cost-effective US\$4.52/LYG and US\$3.77/QALY
Lu, 2013	84.3% for HepB3 and 66.1% for timely HepB1	66% (HBsAg+ HBeAg+) 73% (HBsAg+ HBeAg-) 95% (HBsAg- HBeAg-)	3.6, vaccination cost	2008	3	3	Cost-saving
Jia, 2014	100% (catch up for those who missed newborn vaccination)	N/A	0.34	2013	3	0 or N/S	Cost-effective
Zheng, 2015	50% for direct vaccination and 75% for screening based vaccination	93% (21-29 years) 89% (30-39 years) 80 (40-49 years) 70 (50-59 years)	0.76	2014	3	3	Cost saving for young adults (21-39 years) Without screening: direct BCR = 1.06, societal BCR = 1.42 With screening: direct BCR = 1.19, societal BCR = 1.73 Not cost saving for middle aged adults (40-59 years) Without screening: direct BCR = 0.59, societal BCR = 0.59 With screening: direct BCR = 0.68, societal BCR = 0.43
Chen, 2016	99.6% for HepB3 and 95.88% for timely birth dose	83.1% for vaccine only and 91.0% for vaccine+HBIG (HBsAg+ HBeAg+)	0.5	2013	3	3	Cost saving HepB+HBIG compared with HepB vaccination without HBIG: direct BCR = 0.4, and societal BCR = 2.7

*The Campbell and Cochrane Economics Methods Group (CCEMG) and the Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre) Cost Converter (<http://eppi.ioe.ac.uk/costconversion/default.aspx>)

CBA: Cost-benefit analysis; CEA: Cost-effectiveness analysis; CMA: Cost-minimization analysis; CUA: Cost-utility analysis; DALY: Disability-adjusted life year; QALY: Quality-adjusted life year; LYG: Life year gained; N/A: Not applicable; N/S: Not specified

Prevention of mother-to-child-transmission (PMTCT)

A review assessed the effect of the use of antivirals in pregnancy to reduce hepatitis B viral load and reduce perinatal transmission. It was undertaken as part of scope of work for 2015 WHO Guidelines on Prevention, Care and Treatment of persons with chronic hepatitis B infection. A proportion of infants born to HBsAg+ve mothers acquire HBV despite HBV vaccination; together with growing evidence suggesting that maternal treatment with nucleos(t)ide analogue therapy in 3rd trimester of pregnancy plus vaccine /HBIG for infant may further reduce HBV transmission to the infant. 35 studies were identified (12 RCTs, 19 observational studies and two systematic reviews).

No formal recommendation on use of antivirals for PMTCT was made for 2015 HBV guidelines because: (1) Current limited and low quality evidence base with 3 ongoing (and one completed but unpublished) trials due to report in 2015–2016; (2) Overall, data limited for comparisons of different antivirals, and suitable data were identified only for three different antivirals: lamivudine, telbivudine and tenofovir; and (3) Lack of consensus as to the programmatic implications of a policy of more widespread antiviral use in pregnancy, given very limited access to HBV viral load assays.

There are plans within GHP to update the systematic review on effectiveness data to include additional trials, especially those with tenofovir, and to also seek additional programmatic experience to inform feasibility: (e.g. Access to HBV DNA, HBsAg quantification, HBeAg; Implementation of HBsAg testing and coverage in antenatal clinic setting; Prevalence of HBeAg + and high HBV DNA in different regions/settings and Access to TDF). There is currently no recommendation from the Global Hepatitis Programme. The evidence would be reviewed again in 2017.

Introducing this intervention would potentially require antenatal screening with some measure of viral load. The programmatic requirements of such an approach are likely to be considerable and it would be good to develop documentation of what these might be prior to guidance on use.

It is important to map the proportion of HBsAg positive women of childbearing age who were HBeAg positive and/or HBV DNA positive. This information might be required by region or country (for example there appears to be a marked difference in HBeAg prevalence between China Asia and AfricaSub-Saharan Africa).

Countries that have introduced hepatitis B birth dose

http://www.who.int/immunization/monitoring_surveillance/data/en/

List of WHO Prequalified hepatitis B containing vaccines and licensed schedules:

http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html

Number of births occurring at home: http://www.who.int/maternal_child_adolescent/epidemiology/profiles/maternal/en/

Births attended by skilled health staff (% of total): <http://data.worldbank.org/indicator/SH.STA.BRTC.ZS>

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Annex 1:

Ad-hoc expert consultation on optimizing the hepatitis B vaccination schedule

1–2 September 2016

**Conclusions and recommendations
(28/09/2016)**

Disclaimer: This document has been prepared to inform SAGE deliberations on HBV vaccination schedules. The content of this document includes the conclusions and proposed recommendations by a group of HBV and immunization experts. However, these conclusions and recommendations will only become WHO recommendations if and when SAGE endorses them.

Objectives

- To discuss and review the evidence on hepatitis B vaccine to inform SAGE discussions on optimal schedules and delivery strategies. Evidence will include:
 - Global hepatitis B seroprevalence systematic review.
 - Immunogenicity and efficacy of selected hepatitis B vaccine schedules.
 - Effect of hepatitis B vaccination among immunosuppressed populations
 - Literature review on the thermostability of the hepatitis B vaccines
 - Review of barriers to implement the birth dose.
 - Current and anticipated impact of various vaccination schedules at reducing HBV related disease.
- To outline the conclusions and recommendations that will be presented for SAGE's consideration
 - What are the optimal immunization schedules for hepatitis B vaccines for infants living in different epidemiological settings?
 - Do persons at high risk of inadequate immune response should receive different schedules?
 - What is the incremental effectiveness of implementing a hepatitis B vaccine birth dose (e.g. immunological and clinical outcomes)?
 - Does the available evidence support flexibility in the requirement for cold chain storage of hepatitis B containing vaccines to expand the delivery of the birth dose?

Summary

1. Welcome and Introductions. Dr Okwo-Bele opened the meeting with a presentation summarising the current status of global immunisation highlighting the issues for hepatitis B vaccination.

Dr Hall then noted that this meeting was to address the questions and evidence that should be presented to the SAGE meeting in October.

Dr Okwo-Bele's presentation had highlighted the tremendous success in the Western Pacific Region (WPR) in hepatitis B control. In continuation, Dr Joe Woodring from Manila presented the situation of that Region.

2. **Updated on hepatitis B Control – WPR experience.** In his presentation, Dr Woodring highlighted a number of key issues which had facilitated WPRO success: Political commitment, leadership by the Regional Office, recruitment of expertise globally and formation of an Expert Resource Panel, individual country analyses of issues and their solutions, an emphasis on the birth dose delivery either through deliveries in health institutions or by delivering vaccine outside the cold chain where appropriate and health worker education and vaccination policy. Dr Woodring summarized the progress towards the regional control goal of $\leq 1\%$ of chronic hepatitis b infection. He also discussed the strategies

to improve the birth dose coverage and presented the results of two out of the cold chain pilot studies. Concerns were raised regarding the wastage of vials in one of the study sites. However it was clarified that the pilots used one and 10-dose vials and that the wastage as reduced when the 10-dose vials were not counted.

3. Review of **re-analysis of the HBsAg prevalence**. Professors Edmunds and de la Hoz each presented aspects of a large database re-analysis of prevalence data compiled by Dr Ott and her team. Professor Edmunds described the techniques that he was using to provide estimates for areas with no data available and Prof de la Hoz described the descriptive analysis separating out studies before and after the introduction of vaccination.

Meeting participants noted the value of prevalence data for mathematical modelling exercises and as feedback to the countries themselves. However they noted how sparse post-vaccination data was especially countries outside of the WPR. It was also recommended that antenatal surveys are conducted as they reflect pre-vaccination carriage prevalence for countries with introduction in the last decade as well as they show the probability of perinatal transmission. It was also suggested to generate a data extraction tool to obtain the data points for the future surveys.

4. Review of the **efficacy, effectiveness and safety** from randomized controlled trials and observational studies of childhood schedules using hepatitis B vaccines. Dr Karla Soares-Weiser presented an update of her previous systematic review of the immunogenicity and safety of hepatitis B vaccination schedules. She noted a great paucity of recent studies and that many of the studies in the review were of poor methodological quality as reported.

The meeting noted that the possible schedule are highly flexible in terms of numbers of doses and spacing provided between the various doses delivered early in life.

Data on boosters and long term protection were discussed and it was concluded that the evidence doesn't contradict the current WHO recommendations. It was suggested to note to SAGE that the decline in antibody titre or waning antibodies (anti-HBs) does not imply "loss of clinical protection" as evidenced by increases in anti HBsAg titres following a booster dose (Middleman AB et al 2014; Spradling PR, et. al. Infect Control Hosp Epidemiol. 2015). In addition, the critical point to eliminate hepatitis B is preventing perinatal transmission as most of chronic carriers are attributable to mother-to-infant-transmission (Shimakawa et al 2105.)

It was also suggested to provide a GRADE summary table with the studies on long-term protection and the systematic review.

The need for continued surveillance was highlighted.

5. Special populations – **Low birth weight**. Dr Henao Restrepo provided a summary of the evidence on vaccination and low birth weight babies. This clearly showed the reduced immunogenicity of vaccination in this group. However, the group noted that delaying vaccination would leave the baby at risk. The participants therefore recommended that all babies should have a birth dose whatever their birth weight and those with a low birth weight should start their primary schedule of vaccination 1 month later. Vaccinating all infants at

birth ensures that all babies have some protection in case of positive, unknown or false negative maternal antigen status or exposure in the first month of life.

6. **Special populations – HIV infected persons.** The group had previously discussed an expert review commissioned and undertaken by British Medical Journal Clinical Evidence Group in 2014 and presented by Dr Easterbrook at a previous meeting which concluded a double dose (40 ug) HBV vaccine at 0, 1, 6 months was more clinically effective than the standard regimen with 20 ug in those HIV positive. A further search conducted by Professor de la Hoz in both children and in adults addressed the medium to long term effects of vaccination. This review found that the increase in antibody following higher concentration vaccine was short-lived. It also found that there was no evidence available on the protective effects of vaccine-induced antibody in those HIV positive.
The group concluded that there was no strong evidence to change the current WHO recommendation on vaccination of HIV positive population at any age. Recommending periodical monitoring of anti HBs titres may be discussed at SAGE. Clearly additional research on this issue is needed.
7. **Hepatitis B and hepatitis C attributable liver cancer.** Dr Plummer presented a recently published analysis that assessed the fraction of primary liver cancer by area that could be attributed to HBV and to HCV. This emphasised the large number of cases from these causes in East Asia and in Africa. The group noted the great value of this for advocacy and suggested the possibility of age-stratified analyses to particularly look at potentially preventable cases in the younger ages groups.
8. **Mathematical model.** John Edmunds presented two types of mathematical models. First, a static model using the global prevalence review looking at the likely impact of vaccination country by country. Second, a transmission model applied to data from China, South Korea and The Gambia looking at the long term (over the next century) impact of the hepatitis B vaccination programmes on cirrhosis and primary liver cancer incidence.

The group noted that vaccine alone will not lead to a reduction in persons with disease until the second half of the century. The group noted that this illustrated the continuing need for treatment of existing carriers, cirrhosis and liver cancer.

The model also illustrated the flexibility of the vaccine schedule in as much as the modelling results of any schedule showed a similar estimated impact.

The group noted that the model did not show an early impact because of the population growth which is expected in many countries. However it also noted that data from China clearly showed that the population under ten there is effectively and “infection free generation”.

9. **Evaluation of hepatitis B Vaccination.** Dr Raymond Hutubessy then presented a review of cost effectiveness studies of hepatitis B vaccination in low and middle income countries.

The group noted that these were overwhelmingly favourable with the exception of one study in India which did not find a birth dose cost effective.

It also noted that there was a paucity of studies and that none of them used transmission models and modern methods. It was therefore felt new studies would be valuable, particularly to NITAGs tasked with developing national policies.

10. **Prevention of mother to child transmission.** Dr Philippa Easterbrook presented evidence on the use of antivirals in pregnancy to reduce hepatitis B viral load and reduce perinatal transmission that was undertaken as part of scope of work for 2015 WHO Guidelines on Prevention, Care and Treatment of persons with chronic hepatitis B infection. A proportion of infants born to HBsAg +ve mothers acquire HBV despite HBV vaccination; together with growing evidence suggesting that maternal treatment with nucleo(s)tide analogue therapy in 3rd trimester of pregnancy plus vaccine/HBIG for infant may reduce HBV transmission to the infant. 35 studies were identified (12 RCTs, 19 observational studies and two systematic reviews).

She emphasised that no formal recommendation on use of antivirals for PMTCT was made for 2015 HBV guidelines because: (i) Current limited and low quality evidence base with 3 ongoing (and one completed but unpublished) trials due to report in 2015–2016; (ii) Overall, data limited for comparisons of different antivirals, and suitable data were identified only for three different antivirals: lamivudine, telbivudine and tenofovir; and (iii) Lack of consensus as to the programmatic implications of a policy of more widespread antiviral use in pregnancy, given very limited access to HBV viral load assays.

Dr. Easterbrook highlighted plans within GHP to update the systematic review on effectiveness data to include additional trials, especially those with tenofovir, and to also seek additional Programmatic experience to inform Feasibility: (eg. Access to HBV DNA, HBsAg quantification, HBeAg; Implementation of HBsAg testing and coverage in antenatal clinic setting; Prevalence of HBeAg + and high HBV DNA in different regions/settings and Access to TDF).

The group noted that this intervention would potentially require antenatal screening with some measure of viral load. The programmatic requirements of such an approach are likely to be considerable and the group felt it would be good to develop documentation of what these might be prior to guidance on use.

The group also noted that mapping of the proportion of HBsAg positive women of childbearing age who were HBeAg positive and/or HBV DNA positive by region or country would be useful (for example there appears to be a marked difference in HBeAg prevalence between Asia and Sub-Saharan Africa).

Cost effectiveness analyses would be valuable.

11. **Hepatitis B birth dose coverage.** Dr de la Hoz presented the results of a systematic review on the barriers to implement a birth dose. Among the main barriers perceived by the countries in the AFRO and SEARO regions were the funding for birth dose programmes, the births occurring outside the health facilities, the lack of data on the disease burden, issues on the vaccine storage and cold chain and the central policies and guidelines. This was in agreement with the literature review that in addition noted the health workers' poor knowledge on HBV.

Presentations were made by SEARO and AFRO verbally on the issues that they perceived being obstacles to improving hepatitis B vaccine coverage.

In discussion these obstacles were categorised into:

- Policy/political, coordination challenges between EPI and the Ministries of Health, rationale, advocacy and support for introduction of the birth dose, policy updates, establish and/or reinforce NITAGs.
- Operational, technical support to reach home deliveries, benefits of the use of the out of the cold chain
- Monitoring: data on country coverage and introduction, fear of Adverse events after immunization , data on seroprevalence

The group noted that the definition of birth dose needed to be clarified as it varied across countries and studies. The group also suggested the drafting of a document to support the introduction of the hepatitis b birth dose.

12. **Stability of hepatitis B vaccine.** Since an important proportion of deliveries at home or limited cold chain in peripheral health may hamper access to the birth dose, Dr Brad Gessner presented a review of published data and manufacturers' data that assessed the thermostability of hepatitis B monovalent vaccine. Existing data indicates that most hepatitis B vaccines are heat stable and have been found to maintain immunogenicity after exposure to temperatures of up to +45°C for one week and temperatures up to +37°C and +41°C for several weeks. Field experience suggest there maybe programmatic advantages in keeping hepatitis b vaccine in ambient temperatures at service delivery points, especially as a strategy for reaching home births.
13. **CTC process to on-license us of hepatitis B birth dose in a CTC.** Dr Petit presented on the regulatory process required for pre-qualification of a vaccine, concerns raised by the CTC working group under IPAC regarding OCC off-label vaccine use and a survey of countries in AFRO and WPRO on their desire for a CTC- compatible hepatitis B birth dose vaccine.

The group noted that a CTC pre-qualified vaccine might be more expensive, though so far only one manufacturer has provided this information. The group further noted that and that several countries were already using the vaccine OCC, though except for Indonesia, only on a pilot basis. It proposed that SAGE recommends encouraging CTC pre-qualification whilst recommending the use of vaccine off label for OCC. However, the question was raised how much scientific background and detail was required by SAGE to make a sound and sufficiently informed decision regarding off-label use, and to define the conditions for OCC usage, in terms of temperature and time. It was further recommended to contact those manufacturers who have shared their thermostability data, so as to encourage them to apply for CTC licensure.

14. Preparing for SAGE discussions. The group discussed the questions to be put to SAGE they were:

- Do the current recommendations require any change?
- What is the impact of the vaccination programme in the hepatitis b epidemiology?
- Does the available evidence support flexibility in the requirement for cold chain storage of hepatitis B monovalent vaccine in order to expand the delivery of the birth dose?

15. Next steps

- a. WHO Secretariat to summarize the evidence presented at the meeting and to produce the background document for SAGE.
- b. WHO Secretariat to write a short document on antiretroviral therapies.
- c. WHO Secretariat to produce an overview of the different interventions for different demographic/epidemiological settings.

SCHEDULES AND STRATEGIES FOR HUMAN PAPILLOMAVIRUS (HPV) IMMUNIZATION

1 | POLICY QUESTIONS AND OVERALL CONCLUSIONS

1. *What is the incremental effectiveness and cost-effectiveness for cervical cancer prevention of different HPV vaccines based on girls-only immunization?*

- Current evidence suggests that the three registered vaccines have similar effectiveness for the prevention of cervical cancer associated to HPV types 16/18.
- As per current WHO recommendations, the priority of HPV immunization should remain the prevention of cervical cancer through the immunization of girls, prior to becoming sexually active. The priority age range should be harmonized to that of the extended 2-dose immunization schedule, i.e. 9–14 years. Achieving high coverage among adolescent girls is the priority.
- Introduction of HPV vaccines in national programmes should be *strongly* recommended, while maintaining the current qualifiers.
- At national level, the goal should be to introduce the HPV vaccine country-wide. Phased introductions toward that eventual goal should only be an alternative for those countries that cannot afford or implement operationally an immediate country-wide vaccination programme.

2. *What is the incremental effectiveness and cost-effectiveness for prevention of HPV-related diseases of adolescent gender-neutral HPV immunization compared to girls-only HPV immunization?*

- Vaccination coverage reached in females influences the incremental effectiveness of a gender-neutral immunization. If the vaccination coverage in girls is greater than approximately 70–80%, a gender-neutral immunization that includes adolescent boys becomes less cost-effective than immunization targeting only girls and women aged ≤18 years.
- Nonetheless, tangible benefits of gender-neutral immunization include, but are not limited to, more rapid population level impact (herd effects), indirect protection of unvaccinated women, and direct protection of men who have sex with men.

✓ THIS SUMMARY INCLUDES

1 | Policy questions and overall conclusions 1

2 | Key findings 3

- Burden of cervical cancer and HPV-related cancers
- Relative contribution of different viral types to HPV-related cancers
- Efficacy and immunogenicity of HPV vaccines
- Impact of HPV immunization programmes and herd effects
- Effectiveness and cost-effectiveness of HPV immunization strategies

3 | Summaries of evidence 8

- Burden of HPV-related cancers
- Burden of anogenital warts
- Efficacy and immunogenicity data from RCT of HPV vaccines
- Impact of HPV immunization programmes and herd effects
- Cost-effectiveness of HPV immunization programmes
- Observed impact and herd effects of HPV immunization programmes
- Modelling HPV immunization strategies
- Age at sexual initiation

4 | List of online documents19

5 | Bibliography20

✗ THIS SUMMARY DOES NOT INCLUDE

Detailed information on operational issues

- Gender-neutral immunization could be considered based on elements, such as competing health priorities, disease burden, equity, programmatic implications, cost-effectiveness, and affordability.

3. What is the incremental effectiveness and cost-effectiveness for cervical cancer prevention of immunization of multiple female cohorts (multiple age cohorts within a defined age range) compared to single age cohort immunization of only girls aged 9–13 years or of both girls and boys aged 9–13 years?

- Due to wider direct protection and stronger herd effects, immunization targeting multiple age cohorts would result in faster population impact than immunization of single age cohorts. It should also offer opportunities for economies of scale in delivery and could make programmes more resilient to unintended interruptions in vaccine delivery.
- Immunization of multiple cohorts of girls is cost-effective in the age range of 9–14 years, in particular when the recommended extended 2-dose schedule is used. The incremental cost-effectiveness for each additional age cohort of girls and women aged ≥ 15 years depends on country context because immunization requires a 3-dose schedule and proportionally more girls and women would have already become sexually active.
- Immunization of multiple cohorts of girls aged 9–14 years should be recommended. As with single age cohort immunization, HPV vaccine introductions based on multiple age cohorts will require adequate operational and financial planning.

2 | KEY FINDINGS

Burden of cervical cancer and HPV-related cancers

Estimates are that 630,000 new HPV-related cancer cases occurred in 2012 (**Table 1**). Of those, 570,000 (90%) cases were in women and 61,000 (10%) in men. The 530,000 (84%) cervical cancer cases drive these figures. Accurate HPV prevalence data and cancer incidence rates are lacking for many countries and are a source of uncertainty in particular for the burden of non-cervical cancers and for the burden in men.

Table 1. Cancer cases attributable to human papillomavirus (HPV) estimated for 2012, by cancer site (1, 2)

Anatomical cancer sites (ICD-10 code)	Total incident cases	Total incident cases attributable to HPV	AF	Incident cases attributable to HPV by gender	
				Females	Males
Cervix uteri (C53)	530,000	530,000	100.0%	530,000	0
Vulva (C51)	34,000	8,500	24.9%	8,500	0
Vagina (C52)	15,000	12,000	78.0%	12,000	0
Anus (C21)	40,000	35,000	88.0%	18,000	17,000
Penis (C60)	26,000	13,000	51.0%	0	13,000
Oropharynx (C01, C09–10)	96,000	29,000	30.8%	5,500	24,000
Oral Cavity (C02–06)	200,000	4,900	2.5%	1,700	3,200
Larynx (C32)	160,000	3,800	2.4%	450	3,300
Other Pharynx (C12–C14)	78,000	0	0.0%	-	-
Total	1,200,000	630,000	54.0	570,000	61,000

Notes: Numbers over 100 are rounded to the closest two-digit number; ICD, international classification of diseases; AF, attributable fraction.

Asia accounts for the majority of the 530,000 cervical cancer cases, in particular because of the burden in India and China. However, the highest incidence rates are in Sub-Saharan Africa. Low- and lower-middle income countries account for 291,300 (55%) cervical cancer cases, a burden that is in sharp contrast with the limited access to HPV vaccine by adolescent girls (**Figure 1**).

Figure 1. Comparison of cervical cancer incidence in countries that have and have not introduced HPV vaccine (1, 3, 4)

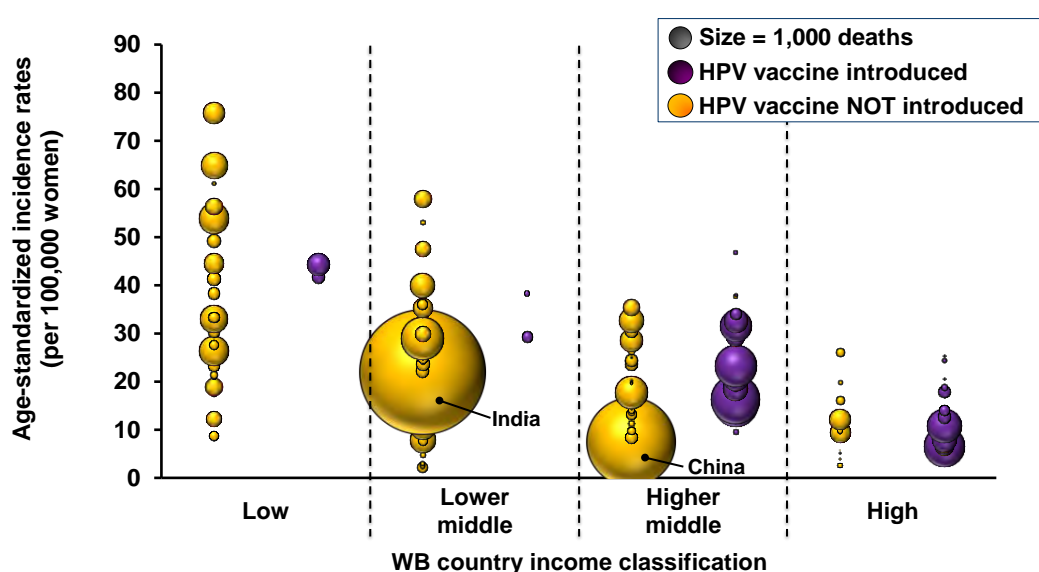


Table 2 provides the 2012 estimated number of cervical cancer cases by country income level and eligibility for GAVI support. For India (a low-middle income and GAVI-eligible country) and China (an upper-middle income and not GAVI-eligible country), 122,844 and 61,691 cervical cases were estimated, respectively.

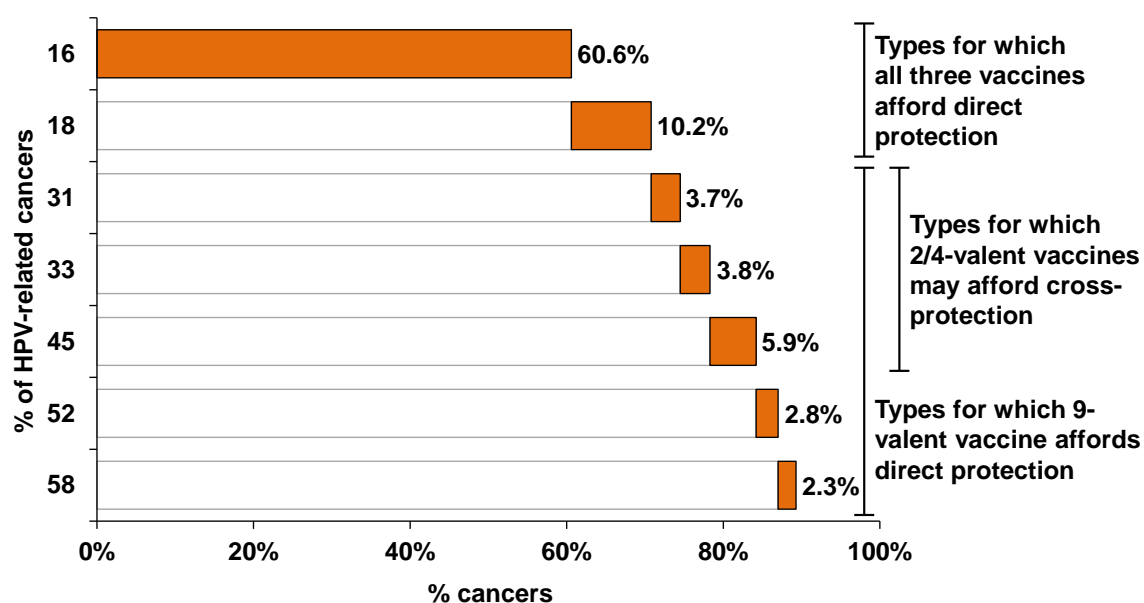
Table 2. Cervical cancer cases estimated for 2012 by country income classification by the World Bank, eligibility for GAVI support, and HPV vaccine introduction (1, 3-5)

Country classification	Cervical cancer cases (% of all cases)		
	Total	In countries that have introduced the HPV vaccine	In countries that have NOT introduced the HPV vaccine
- Country income classification			
-- Low	59,804 (11.4%)	5,281 (1.0%)	54,523 (10.4%)
-- Lower middle	231,462 (44.1%)	1,340 (0.3%)	230,122 (43.8%)
-- Upper middle	169,448 (32.2%)	74,329 (14.1%)	95,119 (18.1%)
-- High	59,698 (11.3%)	50,683 (9.6%)	9,015 (1.7%)
-- Not categorized	4,956 (0.9%)	4,956 (0.9%)	0 (0.0%)
- GAVI support			
-- Eligible	239,158 (45.6%)	5,593 (1.1%)	233,565 (44.5%)
-- Not eligible	286,210 (54.4%)	130,996 (24.9%)	155,214 (29.5%)
Total	525,368 (100.0%)	136,589 (26.0%)	388,779 (74.0%)

Relative contribution of different viral types to HPV-related cancers

HPV is a necessary cause of **cervical cancer**. Globally, HPV 16/18 (the two high-risk types against which all three available HPV vaccines afford direct protection) are associated with 71% of the cases (**Figure 2**). HPV 31/33/45 (three high-risk types against which the bi- and quadrivalent vaccines may afford cross-protection) are associated with 13% of the cases. Lastly, HPV 31/33/45/52/58 (five high-risk types against which only the 9-valent vaccine affords direct protection) are associated with 18% of the cases.

Figure 2. Relative contribution of different viral types to cervical cancer—World, 2012 (6)



Non-cervical HPV-related cancers are more frequently associated to HPV 16/18 than cervical cancer (80% versus 71% of HPV-related cancers, **Table 3**). HPV 16/18 are associated with 85% of head-and-neck cancers and 87% of anal cancers—the second and third more frequent HPV-related cancers with 38,000 and 35,000 estimated cases per year (**Table 6**). On the other hand, non-cervical HPV-related cancers are less frequently associated with HPV 31/33/45/25/58 than cervical cancer (10% versus 19%, **Table 3**).

Table 3. Relative contribution of selected high-risk HPV types to cervical and non-cervical HPV-related cancers

Anatomical cancer site	Cancers attributable to HPV	Estimated number of cancers attributable to (% [by row])		
		HPV 16/18	HPV 16/18/31/33/45/52/58	Difference
		[A]	[B]	[B-A]
Cervix uteri	530,000 (100%)	370,000 (71%)	470,000 (90%)	100,000 (19%)
All other sites	110,000 (100%)	84,800 (80%)	95,300 (90%)	10,500 (10%)
Total	640,000 (100%)	454,800 (71%)	565,300 (90%)	110,500 (17%)

Note: adapted from **Table 6**.

Efficacy and immunogenicity of HPV vaccines

All three HPV vaccines afford strong protection at least against HPV 16/18 infections. Consequently, vaccination with any one of the vaccines is expected to provide substantial public health benefits in terms of prevention of cervical cancer and other HPV-associated cancers.

Data on immunogenicity and protection for clinical endpoints are now available for significant periods of follow-up. Available minimum follow-up periods for the different HPV vaccines are summarized in **Table 4**. Detailed data from a systematic review of randomized controlled trials of HPV vaccine is available in **Appendix 1**.

Table 4. Available minimum follow-up period for immunogenicity and selected cervical endpoints of HPV vaccine clinical trials among young women (7-11)

Endpoints	Available minimum follow-up period		
	2vHPV vaccine	4vHPV vaccine	9vHPV vaccine
Immunogenicity	9.4 years	9.9 years	≥3.5 years
Incident HPV cervical infection	9.4 years	9.9 years	5.5 years
Cervical intraepithelial neoplasia grade 1 or more	9.4 years	9.9 years	5.5 years

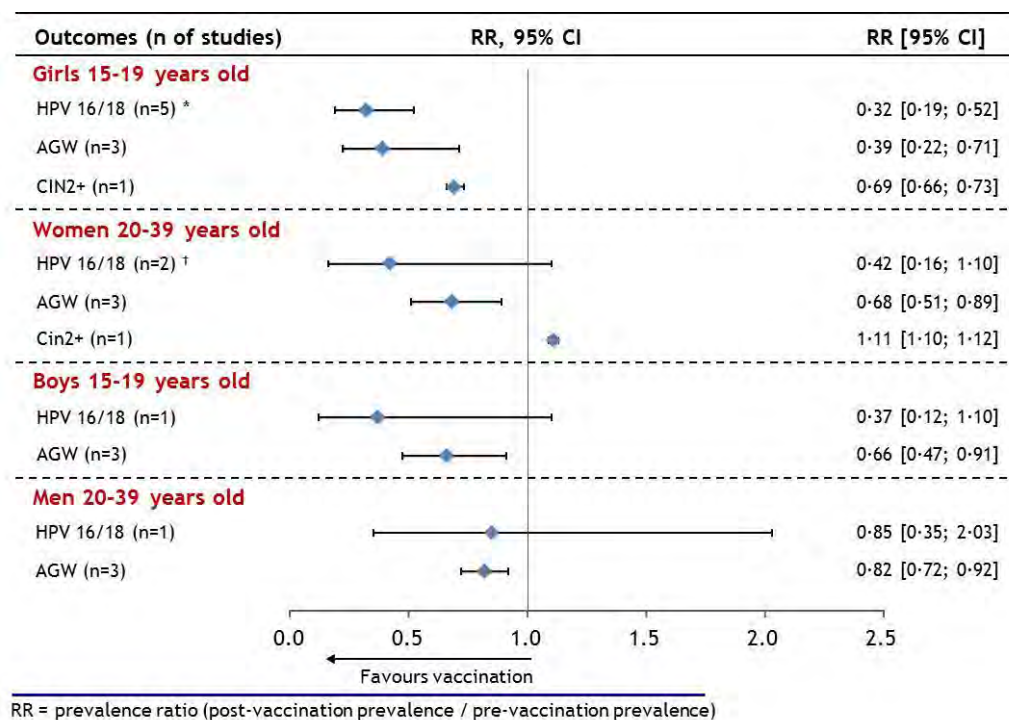
Based on evidence from both randomized clinical trials and post-introduction impact evaluations, the bi- and quadrivalent HPV vaccines provide some level of cross-protection against high-risk oncogenic HPV types other than 16/18, in particular for types 31/33/45. Available follow-up periods are 9.4 and 4.0 years for the clinical trials of the bi- and quadrivalent vaccines, respectively, while they reflect the time from vaccine introduction for impact evaluations (i.e., most data available from year 2009/2010 onwards). (7, 8, 12, 13) Post-introduction impact evaluations are expected to

provide in the near future additional long-term data on this cross-protection, including for endpoints such as cervical intraepithelial neoplasia (CIN) of grade 3.

Impact of HPV immunization programmes and herd effects

High population-level impact and the presence of herd effects were observed in high-income countries after both bi- and quadrivalent HPV vaccination when coverage was $\geq 50\%$ (**Figure 3**). Post-introduction impact data for the 9-valent HPV vaccine are not available yet.

Figure 3. Observed population-level impact and herd effects of girls-only HPV vaccination in high-income countries with coverage $\geq 50\%$ (14)



Effectiveness and cost-effectiveness of HPV immunization strategies

Modelling provides insight into the trade-offs of different HPV immunization strategies. **Figure 4** graphs the modelling estimates of the reduction in prevalence of HPV 6/11/16/18 in infections in women and men for either a gender-neutral immunization at 40% vaccination coverage or a girls-only immunization at 80% vaccination coverage.

In particular, **Figure 4** shows a greater reduction in HPV infection prevalence for both women and men with a girls-only immunization at 80% vaccination coverage than a gender-neutral immunization at 40% vaccination coverage. High coverage for girls only is thus more effective than offering the vaccine to boys. Nonetheless, there may be other tangible benefits to gender-neutral HPV immunization.

Similarly, **Figure 5** graphs the long-term reduction in cervical cancer cases for three different combinations of immunization targeting single or multiple age cohorts and with different age ranges. Compared to the immunization targeting a single age cohort, immunization targeting multiple age cohorts would result in faster effectiveness due to wider direct protection and more rapid herd

effects. As with single age cohort immunization, HPV vaccine introductions based on multiple age cohorts will require adequate operational and financial planning.

Figure 4. Estimated effectiveness of girls-only and gender-neutral HPV immunization depending on vaccination coverage (15)

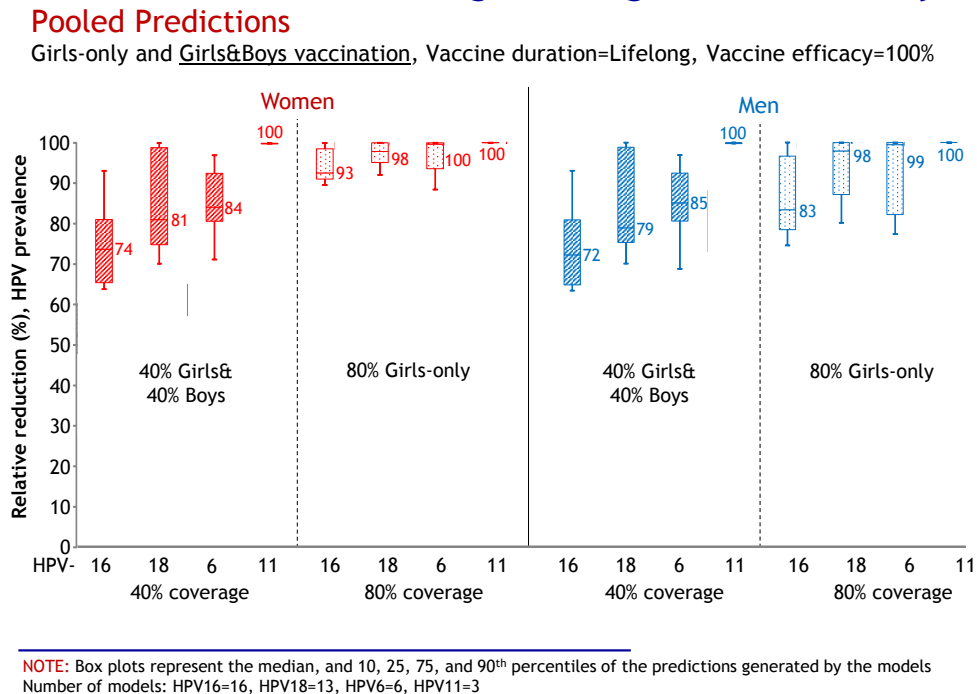
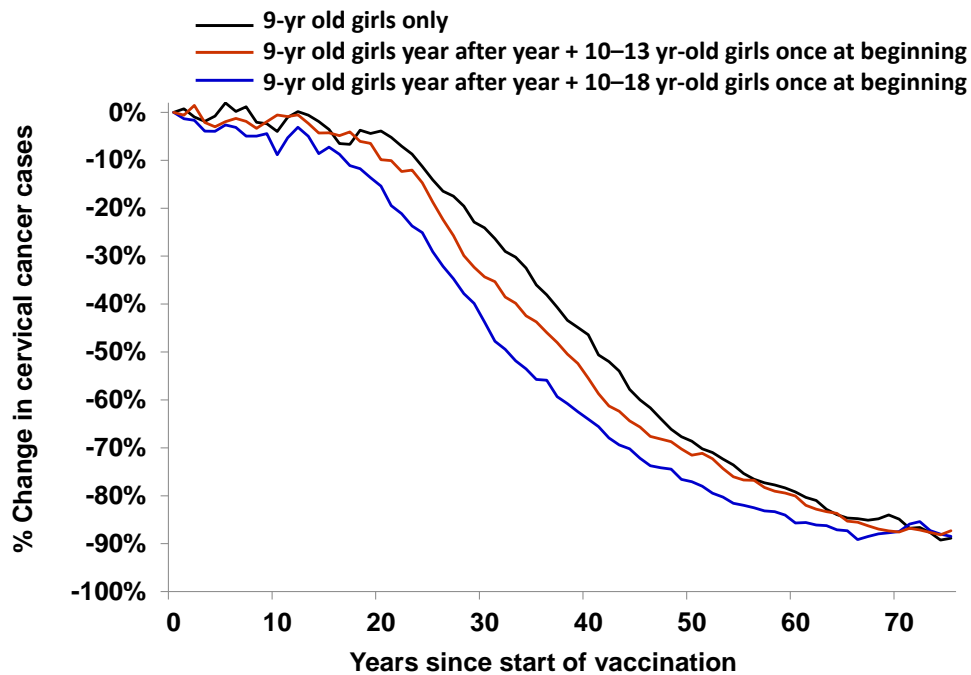


Figure 5. Estimated effectiveness of immunization targeting single and multiple age cohorts (16)



3 | SUMMARIES OF EVIDENCE

Burden of HPV-attributable cancers by anatomical sites, sex, countries and HPV types¹

Introduction. HPV were repeatedly assessed by the International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans (Monographs N°64, 90, and 100B). (17-19) After thoroughly reviewing epidemiological studies and mechanistic studies, the IARC working group classified HPV alpha types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 as carcinogenic to humans (Group 1), and HPV alpha type 68 as probably carcinogenic (Group 2A). These thirteen types are commonly referred to as high-risk or oncogenic types. Cancer sites for which the evidence of HPV involvement is considered sufficient are cervix uteri, vulva, vagina, penis, anus, oral cavity, and oropharynx. The IARC working group also observed that there were positive associations for larynx. Further evidence for larynx has since accumulated and we include it in our list of cancer sites for HPV in our attributable risk estimates.

Methods. Estimates of the number of new cancer cases in 2012 were obtained from GLOBOCAN 2012 version 1.0 and high-quality cancer registries (for rarer cancer types and sub-types). (1) The number of cases due to HPV was calculated by country and then aggregated into eight geographical regions based on the United Nations classification and into WHO regions. The population attributable fraction (AF) for HPV is the proportion of new cancer cases that would have been prevented in a population if all HPV infections had been avoided or successfully treated before they caused cancer. Plummer et al. (2016) described in detail the methods for AF calculation. (2) AFs for each cancer site are summarized in **Table 1**. The relative contribution of HPV 16/18 and HPV 6/11/16/18/31/33/45/52/58 to HPV-associated cancer burden was derived from published meta-analyses. (6, 20, 21) Although HPV 6/11 are not oncogenic in cervical cancer, (18) they were not excluded from the present estimates because of possible involvement in some anogenital carcinomas, notably in the penis. (20) On account of substantial differences in incidence, sex- and country-specific distribution, and methods for causal attribution, the HPV-associated cancers will be assessed separately for: 1) the cervix, 2) other anogenital tract; and 3) head and neck and finally summarized.

Cervical cancer. Cervical cancer accounts for 530,000 cases every year or over 80% of HPV-attributable cancer cases worldwide (**Table 1**). The majority of cervical cancer occurs in the WHO Regions of South-east Asia, Western Pacific, and Africa (in **Table 5** SEARO, WPRO, and AFRO, respectively). HPV 16/18 are the most virulent types and together are responsible globally for 71% of cervical cancer cases. This percentage rises to 90% for HPV 6/11/16/18/31/33/45/52/58 (**Table 6**). The distribution of HPV 16/18 or the nine seven types is similar in women with cervical cancer in different parts of the world, including HIV-positive women. (22, 23) The distribution of HPV types differs however by histology: the contribution of HPV 16 and HPV18 is similar in adenocarcinoma.

Other anogenital cancers. Globally, 8,500 cases of vulvar carcinoma, 12,000 of vaginal cancer, 35,000 of anal cancer (of whom half in men), and 13,000 of penile cancer were attributable to HPV (**Table 1**). As for cervical cancer, the burden of HPV-associated anogenital cancers varies by WHO region but is not larger in less developed regions (**Table 5**). Anal cancer is a relatively rare malignancy but it is one of the most commonly occurring cancers in HIV-positive men who have sex with men. (24) On account of a greater predominance of HPV16 compared to cervical cancer, HPV 16

¹ Prepared by Silvia Franceschi and Martyn Plummer, WHO/IARC, Lyon, France.

and 18 are globally responsible for 87% of anal cancer (**Table 6**). The relative contribution of HPV 6/11/16/18/31/33/45/52/58 is 96%. Vulvar cancers and penile cancers are also relatively rare in all countries and were shown to have different aetiology, with or without active involvement of HPV infection, depending on histological sub-type, age group, and region. (2) The warty-basaloid sub-type and younger patients showed the highest HPV AF. Vaginal cancer is rarer than cancer of the vulva but HPV AF is higher. The relative contribution of HPV 16/18 (approximately 70%) and HPV 6/11/16/18/31/33/45/52/58 (approximately 85%) are similar in vulvar, vaginal, and penile cancer.

Table 5. Cancer cases attributable to human papillomavirus (HPV) estimated for 2012, by anatomical cancer site and WHO region or country development level (1, 2)

WHO region	Total incident cases of all cancers	Total incident cancer cases attributable to HPV	AF	Anatomical cancer site					
				Cervix uteri	Vulva & vagina	Penis	Anus		Head & neck
				Females	Females	Males	Males	Females	Males Females
AFRO	660,000	100,000	15.2%	94,000	2,100	1,000	1,100	1,300	390 170
EURO	3,700,000	97,000	2.6%	67,000	5,400	2,800	3,000	4,500	12,000 2,800
EMRO	550,000	16,000	2.9%	14,000	720	74	480	390	400 210
PAHO	2,900,000	110,000	3.8%	83,000	5,800	3,200	2,800	4,600	8,000 2,200
SEARO	1,800,000	200,000	10.9%	180,000	3,600	4,000	3,100	2,400	7,000 1,400
WPRO	4,400,000	110,000	2.5%	93,000	2,500	2,100	6,800	4,500	3,100 840
Total	14,000,000	630,000	4.5%	530,000	20,000	13,000	17,000	18,000	31,000 7,700

Notes: Numbers over 100 are rounded to the closest two-digit number; AF, attributable fraction.

Table 6. Cancer cases attributable to human papillomavirus (HPV) estimated for 2012, by anatomical cancer site and attributable HPV types (2, 6, 20, 21)

Anatomical cancer site (ICD-10 code)	Total incident cases attributable to HPV	Cases attributable to (%)		
		HPV 16/18	HPV 6/11/16/18/31/33/45/52/58	Difference
		[A]	[B]	[B-A]
Cervix uteri (C53)	530,000	370,000 (71%)	470,000 (90%)	100,000 (19%)
Vulva (C51)	8,500	6,200 (73%)	7,400 (87%)	1,200 (14%)
Vagina (C52)	12,000	7,400 (64%)	9,900 (85%)	2,500 (21%)
Penis (C60)	13,000	9,200 (70%)	11,000 (84%)	1,800 (14%)
Anus (C21)	35,000	30,000 (87%)	33,000 (96%)	3,000 (9%)
Head & neck (C01-06, 09-10,32)	38,000	32,000 (85%)	34,000 (90%)	2,000 (5%)
Total	630,000	460,000 (73%)	570,000 (90%)	110,000 (17%)

Notes: Numbers over 100 are rounded to the closest two-digit number; ICD, international classification of diseases.

Head and neck cancers. Head and neck cancers represent a large and heterogeneous group of malignancies, for which tobacco and alcohol consumption have long been recognized as the predominant causes worldwide. However, a fraction of these cancers, especially in the oropharynx, are caused by HPV (29,000 cases per year of whom 24,000 men) (**Table 1**). The fraction of oropharyngeal cancers attributable to HPV varies greatly being highest in more developed countries (up to 70% in the most recent studies in the USA and some North European countries), but much lower (<20%) and still uncertain in many countries. For cancers of the oral cavity (4,900 cases per year attributed to HPV of whom 3,200 men) and larynx (3,800, of whom 3,200 men), the prevalence of HPV was evaluated only in a few case series. (21, 25) Most of the studies were conducted in Europe and North America, and yielded an average prevalence of approximately 4% at both sites. HPV AF in cancers of the oral cavity and larynx is lower (1–2%) in the rest of the world in which tobacco smoking and chewing are still very common. On account of a greater predominance of

HPV16 compared to cervical cancer, HPV 16 and 18 are globally responsible for 85% of cancer of the head and neck while the relative contribution of HPV 6/11/16/18/31/33/45/52/58 is 90% (**Table 6**).

Limitations. AF for HPV is relatively accurate compared to AF for other infectious agents and, by and large, for lifestyle factors on account of the predominant weight of cervical cancer for which HPV is considered a necessary cause. Substantial limitations of the AFs presented in this report include, however, lack of HPV prevalence data and accurate cancer incidence rates for many countries. In addition, an accurate classification of the site/subsite of cancer origin in the head and neck and the anogenital tract (other than the cervix) is difficult when cancer diagnosis is made in advanced stages and hence the burden of these disease is likely to be underestimated in less developed regions. The relative contribution of the nine HPV types in cervical cancer and other anogenital cancers may be overestimated because of the high frequency of multiple infections especially if newer very sensitive HPV assays are used.

Conclusions. Overall, 640,000 cancer cases are attributable to HPV every year. Wide geographical variation in the fraction of cancers attributable to HPV exists by region, sex, and age group. HPV-attributable cancers account for 8.6% and 0.8% of all cancers in women and men, respectively. HPV AF of all cancers in women ranges from <3% in Australia/New Zealand and the US to 26% in Sub-Saharan Africa. Globally, the relative contribution of HPV 16/18 and of HPV 6/11/16/18/31/33/45/52/58 types is 73% and 90%, respectively (**Table 6**). The population AFs that are shown in this report represent a useful base for prediction models and a potential incentive to act. However, AF should not be confused with the number of preventable cancers, i.e. fraction of cases that can be prevented by specific intervention(s) in a specific time frame.

Burden of anogenital warts²

A systematic review updated and expanded upon a previously published review on the burden of anogenital warts (AGW). The previous review by Fesenfeld et al (2013) included studies that reported incidence, prevalence and self-reported history of AGW in the general adult population, published from January 2001 to January 2012. (26) Abstracts from relevant conferences 2009–2011 were also included. Studies were excluded if the adult population considered did not include at least ages 20 through to 40 years of age or if they focused on immuno-compromised or high-risk populations or children less than 15 years of age. The current review extended the search for publications from January 2012 to June 2016. (27) Inclusion criteria for the updated search were widened: studies were included whether or not they included ages 20–40 and HIV-positive men and women were included as a special interest population. Overall, 44 studies were identified in the search for studies reporting incidence, prevalence and self-reported history and added to the 37 reported in the previous review. Results are summarized by sex, age and HIV-infection status in **Table 7**.

² Edited from a contribution prepared by Brian Buckley, Nicholas Henschke, Nicola Maayan, Rachel Marshall, Vittoria Lutje, and Karla Soares-Weiser, Cochrane Response, London, UK. The original contribution is available online at the SAGE workspace.

Table 7. Burden of anogenital warts (27)

	Both sexes	All ages Men	Women
Incidence (per 100,000 persons)			
- HIV-negative persons of all ages	85–790	77–560	76–1,030
- HIV-negative persons aged ≤30 years	230–790	130–560	320–1,030
- HIV-positive persons	1,389	N/A	N/A
Prevalence (%)			
- All settings	0.019–17.0	0.014–13.7	0.023–10.0
- High detection and prevalence settings omitted	0.019–1.1	0.014–1.3	0.023–0.9
- HIV-positive persons	1.6–17.0	7.3–31	2.8–3.7

For AGW **incidence**, data come from 33 studies, of which only one reported an estimate of incidence in HIV-positive persons. Incidence estimates were higher for studies that included data from settings where AGW detection is more likely (e.g. settings where genital examinations are routine) and/or attending population at greater risk (e.g. sexually transmitted infection clinics). The certainty of the evidence was judged as very low.

For **prevalence**, data come from 27 studies. The certainty of the evidence was judged as very low or low; the most common risks of bias related to case definition, the validity of outcome measurement, and the representativeness of populations and sampling frames.

Finally, 14 studies compared **health-related quality of life**, health status and health utilities amongst people with AGW and amongst people with other HPV-related diseases, healthy controls or population norms. The identified studies suggest that AGW have a significant impact on overall health related quality of life, in particular in terms of anxiety and depression. The factors contributing to the overall decrement in health status measures appear to be primarily associated with anxiety and depression, and to a lesser degree discomfort and pain. The certainty of the evidence was judged as very low or low.

Efficacy and immunogenicity data from randomized controlled trials of HPV vaccines

Three HPV vaccines are licensed and their characteristics are summarized in **Table 8**.

Table 8. Characteristics of licensed human papillomavirus vaccines

Characteristic	Bivalent (2v) vaccine	Quadrivalent (4v) vaccine	9-valent (9v) vaccine
Trade name and manufacturer	Cervarix™, GSK	Gardasil™, Merck	Gardasil9™, Merck
Virus-like particle types (VLP)	16/18	6/11/16/18	6/11/16/18/ 31/33/45/52/58
L1 protein dose	20/20 µg	20/40/40/20 µg	30/40/60/40/ 20/20/20/20/20 µg
System for VLP L1 expression	<i>Trichoplusia ni</i> (Hi-5) insect cell line infected with L1 recombinant baculovirus	<i>Saccharomyces cerevisiae</i> (bread yeast) expressing L1	Same as 4v vaccine
Adjuvant	ASO4 (500 µg aluminum hydroxide, 50 µg 3-O-deacylated-4'- monophosphoryl lipid A)	225 µg AAHS (amorphous aluminum hydroxyphosphate sulfate)	500 µg AAHS

Note: Adapted from Herrero et al. (2015) and Stanley (2016). (28, 29)

In March 2014, a systematic review and meta-analysis of randomized controlled trials of HPV vaccines was submitted for consideration to SAGE. (30) As a result, a 2-dose HPV immunization schedule with a minimum interval of 6 months between doses was recommended for adolescents aged 9–14 years who are not HIV-positive or immunocompromised.

That work was now extended to include trials with female participants that have been published in the meantime as well as, without limitations in time, all trials with male participants regardless of their sexual orientation or whether living with a HIV infection. (31) **Appendix 1** lists the characteristics and findings of the included studies. Nine different comparisons were formally carried out as follows:

- Two doses of HPV vaccine versus three doses of HPV vaccine in younger females (9 to 15 years)
- Longer interval (0, 12 months) versus shorter interval (0, 6 months) of 2-valent HPV vaccine in females
- Two doses of HPV vaccine in younger females (9 to 15 years) versus three doses of HPV vaccine
- 9-valent HPV vaccine versus 4-valent HPV vaccine in females
- HPV vaccines versus placebo (or control vaccine) in males
- HPV vaccines in males versus HPV vaccines in females
- 9-valent HPV vaccine versus 4-valent HPV vaccine in males
- HPV vaccines in men who have sex with men (MSM)
- HPV vaccines in HIV-infected males and females

These formal comparisons, included an evaluation of the quality of evidence based on GRADE, is assembled into a document available online.

Observed impact and herd effects of HPV immunization programmes³

A systematic review updated and expanded upon a previously published review on the population-level impact and herd effects of HPV immunization programmes. The previous review by Drolet et al (2015) included studies published between January 2007 and February 2014. (32) Identical methods were used to update that review with studies published between February 2014 and July 2016. (14)

Studies were eligible if they reported changes, between the pre- and post-vaccination periods, in the incidence or prevalence of at least one HPV-related endpoint: HPV infection, anogenital warts, or CIN grade 2 or higher. Heterogeneity was assessed across studies and trends analysis was performed to examine dose-response association between each study effect measure and HPV vaccination coverage. All analyses were stratified by age and sex and random-effects models were used to derive pooled relative risk (RR) estimates. The pooled estimates presented in the updated review are based temporarily on data collected in the initial systematic review and on descriptive statistics for the newly identified articles.

Table 9 shows the studies included in the original and updated systematic review. Overall, studies were conducted in 12 high-income countries. Although no study examined the impact of HPV vaccination in LMIC, baseline data and/or description of the surveillance system they will be used to

³ Edited from a contribution prepared by Mélanie Drolet, Élodie Bénard and Marc Brisson, Université Laval, Québec, Canada. The original contribution is available online at the SAGE workspace.

document changes over time were identified several countries, such as Bangladesh, Bhutan, China, and Rwanda.

Table 9. Endpoints of the studies systematically reviewed to evaluate the population level impact and herd effects of human papillomavirus (HPV) immunization programmes (14, 32)

Endpoints	Studies identified for the original systematic review (1/2007–1/2014)	Studies identified for the updated systematic review (published 2/2014–7/2016)
HPV infection	7	15 (11 new studies/ 4 updates of previously identified studies)
CIN2+	2	7 (6/1)
AGW	11	8 (5/3)
Total	20	29 (21/8)

Notes: CIN2+, cervical intraepithelial neoplasia grade 2 or higher; AGW, anogenital warts; a study published in the 2 years reports both HPV infection and CIN2+ endpoints.

Additional evidence is emerging on the population-level impact of **girls-only** HPV immunization. In particular, the direct and herd effects of HPV vaccination from the initial review are confirmed in the updated review. All data only refers to bi- and quadrivalent HPV vaccines. In countries with $\geq 50\%$ vaccination coverage of girls, significant decreases between the pre- and post-vaccination periods were observed among girls aged 15–19 years old in rates for HPV 16/18 infections (RR=0.32 [95% CI 0.19–0.52]), CIN2+ lesions (RR=0.69 [95% CI 0.66–0.73]), and anogenital warts (RR=0.39 [95% CI 0.22–0.71]) (**Figure 1**). Significant reductions were also observed for HPV 31/33/45 infections (RR=0.72 [95% CI 0.54–0.96]). Among boys aged 15–19 years (who would be for the vast majority unvaccinated), anogenital warts also decreased significantly (RR=0.66 [95% CI 0.47–0.91]). In this group, recent data from Australia show important but not statistically significant decreases in HPV-16/18 (RR=0.37 [95% CI 0.12–1.10]) and recently published data from England show 30.6% and 25.4% decreases in anogenital warts among 15 to 19-year-old women and men aged, respectively, since the introduction of the bivalent vaccine. Among women aged 20–39 years old (an age groups with lower or absent direct protection from HPV vaccination), significant decreases were observed in anogenital warts (RR=0.68 [95% CI 0.51–0.89]). Among older men, anogenital warts also decreased significantly (RR=0.82 [95% CI 0.72–0.92]). More data for CIN2+ endpoints are becoming available and significant decreases are observed in CIN2+ for girls aged 15–19 years.

Studies on the population-level impact of **gender-neutral** HPV immunization were done for Australia, Canada and USA. However, gender-neutral programmes were implemented recently and the follow-up after the switch from girls-only immunization is limited to 1–2 years. Consequently, it is still too early to measure the additional impact of gender-neutral vaccination at the population-level.

Many countries or territories (Australia, British Columbia in Canada, Denmark, Greece, New Zealand, Norway, Sweden, the UK and the USA) included **catch-up** vaccination in their HPV immunization programmes. However, most of these countries also achieved high coverage in the primary age target of adolescent girls. It is thus difficult at present time to isolate in observational post-introduction impact evaluations the additional population-level impact of vaccinating multiple age cohorts versus that of vaccinating single age cohort.

The systematic review of studies evaluating the impact of HPV immunization programmes shows that HPV immunization is highly effective amongst vaccinated individuals and provides herd effects in settings with high vaccination coverage. This observation reinforces the need for high vaccination

coverage to maximize the population-level impact and herd effects of HPV immunization programmes.

A systematic review and meta-analysis published in October 2016 evaluated changes between pre- and post-vaccination periods in infection rates of high-risk HPV types other than types 16/18. (33) The study included 9 studies with data for 13,886 girls and women aged ≤ 19 years and 23,340 women aged 20–24 years. Among the younger age group, evidence of cross-protection was found for HPV31 (prevalence ratio=0.73 [95% CI 0.58–0.92]) but little evidence of cross-protection for HPV33 and HPV45 (prevalence ratio=1.04 [95% CI 0.78–1.38] and 0.96 [95% CI 0.75–1.23]). The authors concluded that continued monitoring for either decreases or increases in infections rates of non-vaccine high-risk HPV types is important.

Cost-effectiveness of HPV immunization programmes⁴

Literature was systematically searched for cost-effectiveness estimates of various HPV immunization strategies. Twenty-eight studies were included in this systematic review, among which two studies analysed the cost-effectiveness of 9-valent vaccine versus bi- or quadrivalent vaccine, 14 studies conducted the cost-effectiveness analyses of gender-neutral HPV immunization versus female-only immunization, and 15 studies evaluated the cost-effectiveness of single age cohort vaccination of 12-year-old girls combined with multiple age cohort immunization. Three studies analysed both the cost-effectiveness of gender-neutral immunization and multiple age cohort immunization. Key findings are reported here and the full summary is available online. (34) This systematic review extends a previous work by Fesenfeld et al (2013). (26)

Cost-effectiveness of different HPV vaccines in girls-only immunization. Studies that compared the cost-effectiveness of switching from bi- or quadrivalent vaccine to 9-valent vaccine in adolescent females were scarce. The 9-valent vaccine price per dose and the cross-protection provided by HPV vaccine types highly influence the cost-effectiveness analyses. As the price for 9-valent vaccine remains unknown especially in LMIC, the cost-effectiveness of immunization with 9-valent HPV vaccine is still uncertain and more economic evaluations are still needed to understand the true value for money of 9-valent HPV immunization.

Cost-effectiveness of gender-neutral HPV immunization. Almost half of the studies showed that gender-neutral immunization was cost-effective. Vaccine coverage and price play a crucial role in influencing the cost-effectiveness analyses especially in LMIC. If female vaccine coverage is greater than approximately 70–80%, the incremental effectiveness is diminished and gender-neutral immunization that includes adolescent boys becomes less cost-effective than routine vaccination of adolescent girls only. Several existing economic studies fail to account for the broader benefits of HPV vaccination especially among male population such as penile and anal cancers, genital warts and oropharyngeal cancer. Exclusion of these HPV-related male benefits could result in underestimation of the real value of gender-neutral immunization. As such, more cost-effectiveness evidence for gender-neutral immunization is still needed to understand its monetary benefits especially in LMIC.

Cost-effectiveness of vaccinating multiple age cohorts. Most studies reported that immunization targeting multiple age cohorts were cost-effective due to wider primary protection and more rapid

⁴ Edited from a contribution prepared by Nathorn Chaiyakunapruk and Siokshen Ng, Monash University Malaysia. The original contribution is available online at the SAGE workspace.

herd effects. However, the extend of immunization age needs to be interpreted cautiously as several studies analysed the cost-effectiveness of HPV immunization in a single age range only and did not compare in the next age range gradually. The incremental cost-effectiveness for each additional age cohort of girls and women aged ≥ 15 years is expected to decline gradually as more girls and women would have already become sexually active. Above age 15 years, the upper age limit at which HPV immunization stop being cost-effective depends on the country context. Duration of vaccine protection and vaccine price influences the cost-effectiveness of targeting multiple age cohort immunization. If duration of vaccine protection is reduced to a minimum of 10 years, the cost-effectiveness ratio increases and is only cost-effective in the broader age range of immunization, 12–24 years old. Hence, further economic evidences on immunization based on multiple age cohorts are still required especially in LMIC and also in determining the most cost-effective age limit of HPV vaccination.

Effectiveness and cost-effectiveness modelling of HPV immunization strategies

Modelling methods and estimated effectiveness are available online under the supplemental material for the SAGE meeting.

Age of sexual initiation

Several resources are available on age at sexual initiation specifically for LMIC.

An analysis of demographic health surveys published in September 2012 compared national trends in adolescent reproductive and sexual. (35) This analysis included also the percentage of people who had had sexual intercourse by age 15 years in 37 LMIC (**Figure 6**). For most countries, $\leq 15\%$ of adolescents would have had sexual intercourse by age 15 years. The analysis also reports data on age-mixing in sexual relationships (e.g., adolescent women who had sex with partners who were ≥ 6 years older).

Chandra-Mouli et al. (2014) also reported that sexual activity of adolescents varies markedly for boys and versus girls and by region. (36) **Table 10** shows the percent of people aged 20–24 years in 12 LMIC who reported having had sexual intercourse by ages 15 and 18 years.

Actual distribution of adolescents who are sexually active by a specific age can also be found. For instance, Zaba et al. (2004) reported data for Kenya and Uganda (**Figure 7**). (37)

Finally, UNAIDS launched in July 2016 a website that reports information on men who have sex with men. The data include estimates of population size and HIV prevalence. The site is accessible at www.aidsinfoonline.org.

Table 10. Report of sexual intercourse by ages 15 and 18 years reported by people aged 20–24 years in 12 LMIC (36)

Region/country, year of survey	% respondents reporting having had sexual intercourse by age			
	15 years		18 years	
	Male	Female	Male	Female
Sub-Saharan Africa				
- Ghana, 2008	5	7	27	41
- Mali, 2006	4	26	27	73
- Tanzania, 2010	6	15	40	58
- Zimbabwe, 2010-11	4	4	23	38
Asia/Central Asia				
- Azerbaijan, 2006	1	1	22	12
- Bangladesh 2011	1	28	6	64
- Cambodia, 2010	0	1	4	15
- India, 2005-06	-	13	-	43
Latin America/Caribbean				
- Brazil, 1996	33	10	75	43
- Dominican Republic, 2007	27	16	72	51
- Haiti, 2012	35	13	77	51
- Peru, 2012	-	7	-	43

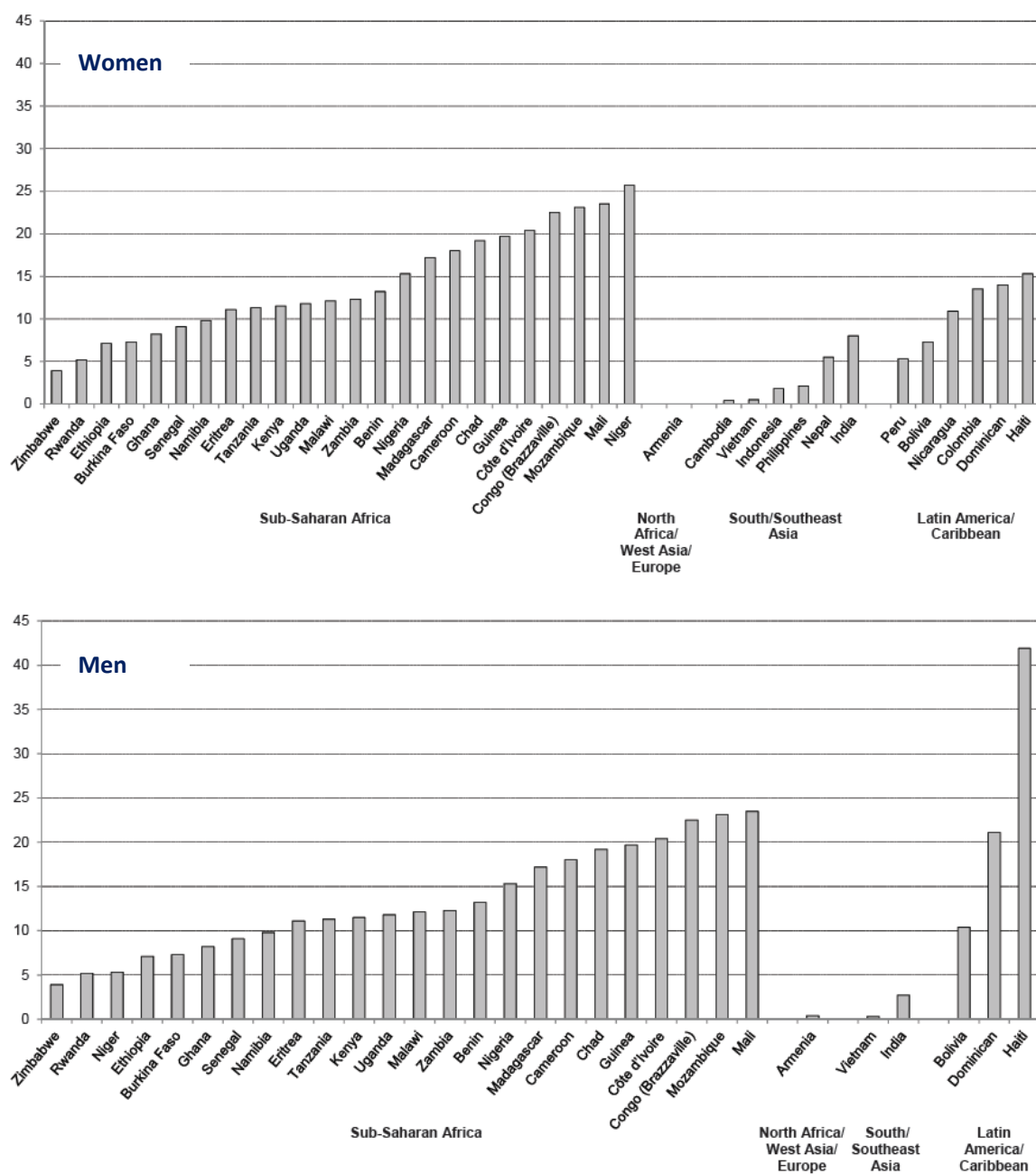
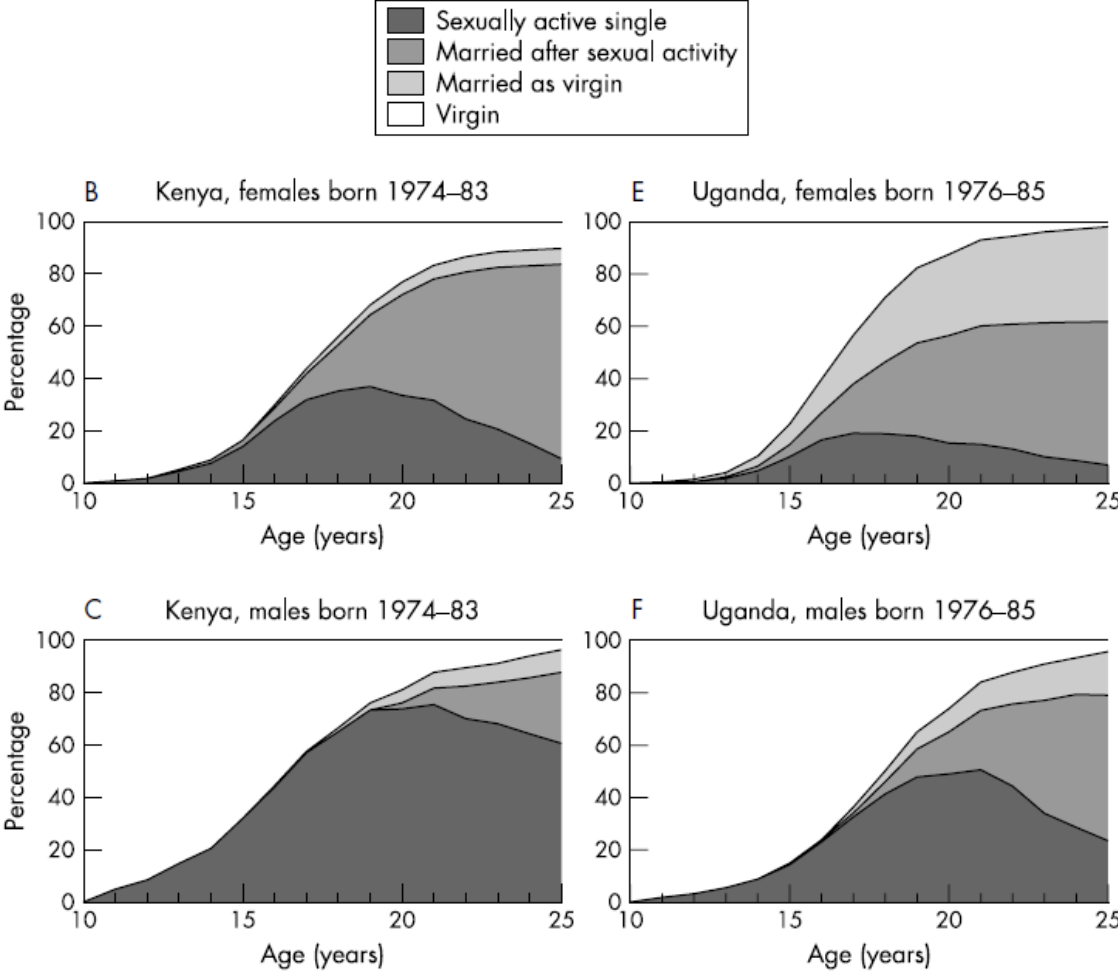
Figure 6. Percentage of adolescents aged 15–19 years who have had sexual intercourse by age 15 years (35)

Figure 7. Percentage of females and males aged 10–25 years of Kenya and Uganda who were sexually active, by marital status (37)



4 | LIST OF SUPPORTING DOCUMENTS AVAILABLE ONLINE

- Global burden of cancers attributable to infections in 2012: a synthetic analysis, 8 pages (2)
- Systematic review of the burden of anogenital warts, 18 pages (27)
- Systematic review of clinical trials of HPV vaccines, 119 pages (31)
- Systematic review of population-level impact and herd effects of HPV immunization programmes, 9 pages (14)
- Systematic review of cost-effectiveness analyses of HPV immunization programmes, 9 pages (34)
- Modelling methods and estimated effectiveness of various HPV immunization strategies
- Statements by WHO GACVS on the safety of HPV vaccines, 2013–2016, 14 pages

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APPENDIX

Appendix 1. Summary of evidence from randomized controlled trials of human papillomavirus virus identified in the update and extension of the systematic review done by D'Addario et al. (2014)

Topic	Reference	HPV vaccine	Setting	Population	Intervention	Outcome	Summary of finding	Evidence certainty
2 doses in younger females vs. 3 doses in older females	Romanowski et al, 2011, 2014 & 2016	2v	Canada & Germany	9 to 25-year old females [124 participants]	2 doses (0.6m) in females aged 9–14 years vs. 3 doses (0.1,6m) in females aged 15–25 years	Immunogenicity	Similar GMTs for HPV 16/18 at 60-month follow-up	VERY LOW
2 doses in younger females vs. 3 doses in older females	Lazcano Ponce et al, 2014	2v	Mexico	9 to 25-year old females [1,526 participants]	2 doses (0.6m) in females aged 9–10 years vs. 3 doses (0.1,6m) in females aged 18–24 years	Immunogenicity	<ul style="list-style-type: none"> Higher GMTs for HPV 16/18 up to 21-month follow-up Similar seropositivity for HPV 16/18 one month after last dose (at 7-month follow-up) 	LOW (GMTs) MODERATE (seropositivity)
2 doses in younger females vs. 3 doses in older females	Puthanakit et al, 2016	2v	Canada, Germany, Italy, Taiwan, and Thailand	9 to 25-year old females [1,032 participants]	2 doses (0.6m) in females aged 9–14 years vs. 3 doses (0.1,6m) in females aged 15–25 years	Immunogenicity	<ul style="list-style-type: none"> Similar or higher GMTs for HPV 16 and 18, respectively, one month after last dose (at 7-month follow-up) Similar seropositivity for HPV 16/18 at 12-month follow-up 	LOW (GMTs) MODERATE (seropositivity)
2 doses in younger females vs. 3 doses in older females	Hernández-Ávila et al, 2016	4v	Mexico	9 to 26-year old females [300 participants]	2 doses (0.6m) in females aged 9–10 years vs. 3 doses (0.2,6m) in females aged 18–24 years	Immunogenicity	Non-inferior GMTs for HPV 6/11/16/18 at 21-month follow-up	LOW (HPV 6) MODERATE (HPV 11/16/18)
2 doses in younger females vs. 3 doses in older females	Dobson et al, 2013	4v	Canada	9 to 26-year old females [569 participants]	2 doses (0.6m) in females aged 9–13 years vs. 3 doses (0.2,6m) in females aged 16–26 years	Immunogenicity	<ul style="list-style-type: none"> Higher GMTs for HPV 11/16 and similar for HPV 6/18 at 36-month follow-up Similar seropositivity for HPV 6/11/16/18 at 36-month follow-up 	VERY LOW (LOW/MODERATE at earlier follow-ups)
2 doses in younger females	Data from vaccine manufacturer presented at a	9v	14 countries	9 to 26-year old females [600 participants]	2 doses (0.6m) in females aged 9–14 years vs. 3	Immunogenicity	Higher GMTs and similar seropositivity for HPV 6/11/16/18/31/33/45/52/58 one month after last	MODERATE

Topic	Reference	HPV vaccine	Setting	Population	Intervention	Outcome	Summary of finding	Evidence certainty
vs. 3 doses in older females	national NITAG				doses (0,2,6m) in females aged 16–26 years		dose (at 7-month follow-up)	
2 vs. 3 doses in younger females	Leung et al, 2015	2v & 4v	France, Hong Kong, Singapore, Sweden	9 to 14-year old females [1,074 participants]	2 doses (0,6m) of 2v vaccine vs. 2 (0,6m) or 3 doses (0,2,6m) of 4v vaccine in girls of same age	Immunogenicity	Higher GMTs for 2 doses of 2-valent vaccine and similar seropositivity for HPV 16/18 at 12-month follow-up	LOW (GMTs HPV 16) MODERATE (GMTs HPV 18) HIGH (seropositivity)
2 vs. 3 doses in younger females	Sankaranarayanan et al, 2016	4v	India	10 to 18-year old females [17,729 participants]	3 doses (0,2,6m), 2 doses (0,6m), 2 doses (0,2m), and single dose	Immunogenicity & efficacy for incident and persistent cervical infection	<ul style="list-style-type: none"> Cluster-randomised trial that lost randomization due to events unrelated to study; data were analysed as an observational study Antibody titres of 3-dose and 2-dose (0,6m) groups show similar decay kinetics and were similar up to 48-month follow-up Frequency of incident HPV 6/11/16/18 infections was similar irrespective of the number of vaccine doses received 	N/A
Interval between doses	Puthanakit et al, 2016	2v	Canada, Germany, Italy, Taiwan, and Thailand	9 to 14-year old females (seronegative at baseline) [965 participants]	12- vs. 6-month interval in 2-dose schedule	Immunogenicity	Higher GMT for HPV 16/18 with longer interval between doses, but similar seroconversion rates for HPV 16/18 one month after last dose	MODERATE
9- vs. 4-valent in females	Vesikari et al, 2015	9v	Belgium, Denmark, Finland, Italy, Spain, Sweden	9 to 15-year old females [600 participants]	3 doses (0,2,6m) of 9- vs. 4-valent vaccine in younger girls	Immunogenicity	<ul style="list-style-type: none"> Similar GMTs for HPV 6/11/16/18 and higher for HPV 31/33/45/52/58 at one month after last dose (at 7 month follow-up) Similar seropositivity for HPV 6/11/16/18, but reference did not report in full seropositivity rates for 4-valent vaccine control group for HPV 31/33/45/52/58 at one 	MODERATE (GMTs and seropositivity for HPV 6/11/16/18) LOW (for seroconversion for HPV 31/33/45/52/58)

Topic	Reference	HPV vaccine	Setting	Population	Intervention	Outcome	Summary of finding	Evidence certainty
9- vs. 4-valent in females	Joura et al, 2015	9v	17 countries	16 to 26-year old females [14,215 participants]	3 doses (0,2,6m) of 9-valent vaccine in younger girls	Immunogenicity and efficacy for persistent infection, CIN, VIN and VaIN	<p>month after last dose (at 7 month follow-up)</p> <ul style="list-style-type: none"> Similar GMTs for HPV 6/16, lower for HPV 11, and higher for HPV 18/31/33/45/52/58 at 24-month follow-up Similar seropositivity for HPV 6/11/16 and higher for HPV 18/31/33/45/52/58 at 24-month follow up No differences in efficacy for HPV 6/11/16/18 and condyloma, higher efficacy for persistent infection, CIN2/3 or worse, VIN/VaIN 1-2/3 or worse at 24-month follow-up 	<p>HPV 6/11/16/18: MODERATE</p> <p>LOW (CIN2/3 and worse, condyloma)</p> <p>HPV 31/33/45/52/58: MODERATE</p> <p>LOW (VIN1/VaIN1 and worse)</p>
Vaccines vs. placebo in males	Petaja et al, 2009	2v		10 to 18-year old males [270 participants]	3 doses (0,1,6m) of 2-valent vaccine vs. control vaccine	Immunogenicity	No data about effects of 2-valent vaccine on GMTs or seropositivity because no placebo data were reported for this outcome	VERY LOW
Vaccines vs. placebo in males	Giuliano et al, 2011 Hillman et al, 2012	4v	18 countries	16 to 26-year old males [4,065 participants]	3 doses (0,2,6m) of 4-valent vaccine vs. placebo	Immunogenicity and efficacy for external genital lesions, condyloma acuminatum, persistent HPV 6/11/16/18 infections, and PIN	<ul style="list-style-type: none"> Lower rates of external genital lesions (any or by HPV 6/11/16/18, condyloma acuminatum, persistent HPV 6/11/16/18 infections) in vaccine group and similar rates for PIN at 2.9-year median follow-up Higher GMTs and seropositivity for HPV 6/11/16/18 at 36-month follow-up No comparison on seropositivity/seroconversion possible because no placebo data reported for this outcome 	<p>MODERATE</p> <p>LOW (PIN, seropositivity)</p>
Vaccines in males vs. in	Lehtinen et al, 2015	2v	Finland	12 to 15-year old males [1,695 participants]	3 doses (0,1,6m) of 2-valent vaccine	Immunogenicity	Similar GMTs and seropositivity for HPV 16/18 at 3.5-year follow-up	LOW

Topic	Reference	HPV vaccine	Setting	Population	Intervention	Outcome	Summary of finding	Evidence certainty
females					in males vs. in females			
Vaccines in males vs. in females	Reisinger et al, 2007 Ferris et al, 2014	4v	10 countries	9 to 15-year old males [1,167 participants]	3 doses (0,2,6m) of 4-valent vaccine in males vs. in females	Immunogenicity and efficacy for persistent infection	<ul style="list-style-type: none"> Similar persistent infection rates for HPV 6/11/16/18 at 8-year follow-up GMTs for HPV 6/11/16/18 initially similar or higher for males than females, but with increasing follow-up time similar or higher for females Similar seropositivity for HPV 6/11/16/18 at 18-month follow-up 	<p>VERY LOW (persistent infection)</p> <p>LOW (GMTs)</p> <p>MODERATE (seropositivity)</p>
Vaccines in males vs. in females	Van Damme et, 2015	9v	24 countries	9 to 15-year old males [3,066 participants]	3 doses (0,2,6m) of 4-valent vaccine in males vs. in females	Immunogenicity and efficacy for persistent infection	<ul style="list-style-type: none"> Similar GMTs for HPV 6/11/16/31/52 and higher GMTs for HPV 18/33/45/58 at 3-year follow-up Similar seropositivity rates for all 9 HPV types at 3-year follow-up 	LOW
Vaccines in males vs. in females	Data from vaccine manufacturer presented at a national NITAG	9v	14 countries	9 to 26-year old females [600 participants]	2 doses (0, 6m) in males aged 9–14 years vs. 3 doses (0,2,6m) in females aged 16–26 years	Immunogenicity	Similar seropositivity for HPV 6/11/16/18/ 31/33/45/52/58 one month after last dose (at 7-month follow-up)	MODERATE
Vaccines in males vs. in females	Castellsagué et al., 2015	9v	17 countries	16 to 26-year old males and females [2,200 participants]	3 doses (0,1,6m) in males vs. in females	Immunogenicity	Higher GMTs and similar seropositivity rates for HPV6/11/16/18/31/33/45/ 52/58 one month after last dose (at 7-month follow)	MODERATE
9- vs. 4-valent vaccines in males	Van Damme et, 2016	4v & 9v	Belgium	16 to 26-year old males (seronegative at baseline) [454 participants]	3 doses (0,1,6m) of 9-vs. 4-valent vaccines	Immunogenicity	<ul style="list-style-type: none"> Higher GMTs for HPV 6/31/33/45/52/58, but similar GMTs for HPV11/16/18 one month after last dose (at 7-month follow-up) Higher seroconversion rates for HPV6/31/33/45/52/58, but similar seroconversion rates for HPV 6/11/16/18 one month after last dose (at 7-month follow-up) 	HIGH

Topic	Reference	HPV vaccine	Setting	Population	Intervention	Outcome	Summary of finding	Evidence certainty
Men who have sex with men (MSM)	Palefsky et al, 2011	4v	Australia, Brazil, Canada, Croatia, Germany, Spain, USA	16 to 26 year-old MSM (seronegative at baseline) [602 participants]	3 doses (0,2,6m) vs. placebo	Efficacy for persistent anal infection, anal intraepithelial neoplasia (AIN), and genital warts	<ul style="list-style-type: none"> Reduced incidence of persistent infection by HPV6/11/16/18 and of AIN2/3 at 2.9-year follow-up Similar incidence of AGW over 2.9-year follow-up 	MODERATE LOW (persistent hpv11 infection and genital warts)
Men who have sex with men (MSM)	Castellsagué et al, 2015	9v	17 countries	16 to 26-year old MSM, men who have sex with women (MSW) and females (seronegative at baseline) [313 MSM, 1,106 MSW, 1,101 women]	3 doses (0,1,6m) in MSM vs. females or MSW	Immunogenicity	<ul style="list-style-type: none"> Compared to females, lower GMTs for HPV6/11/16/31/33/45/52/58, but similar GMTs for HPV18 one after last dose (at 7-month follow) Compared to MSW, lower GMTs for all 9 HPV types Compared to females and MSW, similar rates of seropositivity for all 9 HPV types 	MODERATE
Men and women living with HIV	Levin et al, 2010 Weinberg et al, 2012	4v	USA, Puerto Rico	7 to 11-year old males and females (seronegative at baseline) [90 and 27 persons in vaccine and control groups, respectively]	3 doses (0,2,6m) vs. placebo	Immunogenicity	Higher GMTs and seroconversion rates for HPV 6/11/16/18 with 4-valent vaccine at 24-month follow-up and one month after last dose, respectively	MODERATE
Men and women living with HIV	Denny et al, 2013	2v	South Africa	18 to 25-year old females (mixed sero-status at baseline) [42 HIV-infected and 22non-infected women]	3 doses (0,1,6m) in HIV-infected vs. non-infected women	Immunogenicity	<ul style="list-style-type: none"> Lower GMTs for HPV 16/18 in HIV-infected women one month after last dose (at 7-month follow) Similar seroconversion rates for HPV 16/18 at 12-month follow-up 	LOW
Men and women living with HIV	Toft et al, 2014 Faust et al, 2016	2v & 4v	Denmark	18+ year old HIV-infected males and females (seronegative at baseline) [92 participants]	3 doses 80,1/2,6m) of 4- vs. 2-valent vaccines	Immunogenicity	<ul style="list-style-type: none"> Similar GMTs for HPV16/18 at 12-month follow-up Similar seroconversion rates for HPV 16; seroconversion rates for HPV 18 lower with 4-valent vaccine at 12-month follow-up 	MODERATE

Executive Summary: October 2016 SAGE Session on Yellow Fever Vaccines

Introduction

Yellow fever (YF) cannot be eradicated but epidemics can be eliminated if population immunity levels are heightened and maintained. A three-pronged approach of adding the YF antigen to routine immunization programmes; preventive mass vaccination in at-risk countries/populations; and rapidly responding to outbreaks has successfully controlled the disease in West Africa since 2010. However, recent outbreaks in East and Central Africa highlighted the need to revisit and expand the control strategy and highlighted the need for vaccine supply surge capacity, as the global stockpile became exhausted, and the ability to immunize at-risk populations was in jeopardy. This SAGE session is divided into two sections. The first sub-session is dedicated to WHO's new strategic approach to YF, called "Global Strategy for Eliminating Yellow fever Epidemics (EYE)". This section takes a long term view for how to effectively prevent YF epidemics. The second sub-session addresses issues of vaccine surge capacity in response to major outbreaks. Acknowledging that there are risks for vaccine demand that may exhaust vaccine supply, as experienced in 2016, there is a need to have on hand options for surge capacity (e.g. stockpiling, bulk storage, and dose fractioning). Focus will be on the fractional dose strategy that was used in a recent preventive vaccination campaign in Kinshasa, Democratic Republic of Congo.

SAGE previously reviewed the evidence for YF vaccines in April 2013, which resulted in a revised Vaccine Position Paper published in July 2013.

Purpose of Session

- SAGE is asked to provide feedback on the general approach of the "Global Strategy for Eliminating Yellow fever Epidemics (EYE)".
- SAGE is asked to provide recommendations and research priorities for fractional dose use of YF vaccine as a response to major outbreaks.

Overview of Background Documents in Yellow Book

1) *Global Strategy for Eliminating Yellow fever Epidemics (EYE)*

This document proposes a global and comprehensive long term (2017-2026) strategy able to target the most vulnerable countries and regions, address global risk by building resilience in urban centres and preparedness in areas with potential for outbreaks, while ensuring reliable vaccine supply by forming a global coalition of partners to predict needs and shape vaccine production. The Gavi Programme and Policy Committee (PPC) will review this document together with SAGE feedback at the end of October, and the revised version will be submitted to the Gavi Board in December 2016. SAGE is asked to provide feedback on the strategy outlined in this document.

2) *Fractional dose yellow fever vaccine as a dose-sparing option for outbreak response: WHO Secretariat Information Paper (July 2016)*

This secretariat paper was written in June 2016 and was reviewed by YF experts and SAGE to inform the use of fractional dose in the August 2016 mass vaccination campaign. The

underlying evidence base has not changed. The document reviews the existing evidence on dose-sparing strategies through fractional dosing of YF vaccine as an immediate and short-term option in response to eventual large scale campaign needs, and makes recommendations for fractional dose vaccination in case of imminent need. Updated information to what was known in June 2016 is provided through the Report from DRC Yellow fever campaign (#3 below). Technical annexes to the document with additional evidence are posted on the meeting's website. SAGE is asked to update recommendations with consideration of those outlined in Section 13 of this document.

3) *Yellow fever mass vaccination campaign using fractional dose in Kinshasa, DRC*

In August 2016, a preventive YF vaccination campaign was undertaken in Kinshasa and along the DRC-Angola border. In Kinshasa, a 1/5 fractional dose was administered subcutaneously to individuals 2 years of age and older. This brief report summarizes the experience with fractional dose in Kinshasa, including challenges and lessons learned. This document is for information.

4) *Short-term research priorities for dose-sparing of YF vaccine*

While the current scientific data on fractional dose support WHO's recommendations, important data gaps remain, such as fractional-dose performance in infants, applicability to all WHO-prequalified vaccines, and persistence of neutralizing antibody. Some of this information can be obtained in the near term, while other information would require long-term follow up. The priorities listed in this document focus on the most important short term objectives. SAGE is asked to review and provide suggestions to the research priority document.

Additional Documents on Web

- 1) *Eliminating Yellow fever Epidemics: Yellow Fever Long Term Strategy with Annex*
- 2) *Fractional dose yellow fever vaccine as a dose-sparing option for outbreak response: WHO Secretariat Information Paper with Annex*
- 3) *Vaccines and vaccination against yellow fever WHO Position Paper – June 2013*



Global Strategy to Eliminate Yellow fever Epidemics (EYE)

Document for SAGE – 26 September 2016

Executive summary

The global health community is facing an increased risk of urban outbreaks of yellow fever. Yellow fever's changing epidemiology, a resurgence of mosquitoes and the risk of international spread pose an emerging global threat that requires new strategic thinking.

This document describes the reasoning behind and need for an updated, long-term (2017-2026) and global (Africa and Americas) strategy to "Eliminate Yellow fever Epidemics" (EYE). It includes **three strategic objectives**: (1) protect at-risk populations; (2) prevent international spread; and (3) contain outbreaks rapidly. The strategic approach is comprehensive. In addition to recommending vaccination activities, it calls for building resilient urban centres, planning for urban readiness, and strengthening the application of International Health Regulations

The EYE strategy targets the countries and regions that are considered most vulnerable to outbreaks of yellow fever. The classification of countries' risk has been revised to take into account criteria associated with the changing epidemiology such as environmental factors, population density and vector prevalence.

In all, 27 countries in Africa and 13 in the Americas are considered to be at highest risk and need large-scale, preventive vaccination strategies to establish and maintain high levels of immunity among their populations. In Africa, 5 countries still need to introduce the vaccine into their routine immunization schedules and 12 countries should conduct national mass preventive campaigns. All countries in the Americas have introduced the vaccine into routine vaccination programmes, but 11 of the countries should plan to carry out catch-up campaigns to boost levels of immunity among unprotected pockets among their populations.

Rapid containment of outbreaks is essential to ensure they do not amplify into devastating epidemics. To enhance early detection of cases, surveillance needs to be strengthened. That will require improving laboratory capacity, building on existing surveillance networks and extending the currently limited laboratory diagnostic in-country options.

A revolving mechanism will be put in place to give countries facing emergency needs for yellow fever vaccine access to the internationally managed stockpile. The proposed initial quantity to be held in reserve has been set at 6 million doses and will need to be closely managed in collaboration with vaccine manufacturers. Any outbreak response will include not only reactive vaccination programs, but rapid detection of cases, good case management, vector control and community mobilization -- all elements that need to be strengthened.

Over the coming decade, vaccine manufacturers are expected to be able to meet the global demand of 1.38 billion doses needed to end YF outbreaks. This will require pushing their production to the maximum possible levels, particularly in the first 5 years.

Vaccine needs for the Global Strategy to Eliminate Yellow fever Epidemics, 2017–2026

Routine immunization		Million doses
	Africa	465
	Latin American and the Caribbean	96
Mass campaigns		
	Africa	490
	Latin American and the Caribbean	39
	Brazil	234
Emergencies		60
Total		1384

Cross-cutting core support activities will be initiated from the start of EYE to ensure success through (1) availability of accessible, affordable vaccines procured in a sustained vaccine market, and mechanisms to cope with surges in YF vaccine demand; (2) political commitment at regional and country levels fostered by strong advocacy; (3) robust governance and strong monitoring; and (4) research to support better tools and informed practices.

The EYE strategy will succeed by engaging multidisciplinary partners and coordinating efforts well. But it will require the collaboration of a number of agencies. No country or institution can address this global issue alone.

Acronyms and definitions

ELISA	Enzyme-Linked Immunosorbent Assay
EPI	Expanded Programme on Immunization
FNV	French Neurotropic Vaccine
Gavi	Gavi, the vaccine Alliance
ICG	International Coordinating Group for vaccine provision
IHR	International Health Regulations (2005)
LAC	Latin America and the Caribbean
PCR	Polymerase Chain Reaction
PI	Population Immunity
PMVC	Preventive Mass Vaccination Campaign
PRNT	Plaque Reduction Neutralization Test
RI	Routine Immunization
SAGE	Strategic Advisory Group of Experts on Immunization
TAG	Technical Advisory Group
UNICEF	United Nations Children's Fund
UNPD	United Nation Population Division
VIS	Vaccine Investment Strategy
WHO	World Health Organization
WUENIC	WHO/UNICEF Estimates of National Immunization Coverage
YF	Yellow Fever
YFI	Yellow Fever Initiative

Contents

Executive summary	2
Acronyms and definitions.....	4
Part 1: Introduction and context	7
Lessons learnt from recent YF control programmes	8
Routine immunization: obstacles to progress.....	9
Current implementation of vaccination in Africa and LAC	11
Part 2: Public health tools for YF prevention and control	14
1. YF disease surveillance	14
2. Vector surveillance and control.....	15
3. Vaccination against YF	16
4. Targeting travellers and improving IHR adherence	19
Part 3: Evolution of the global YF risk.....	22
Recent changes in transmission dynamics	22
Risk specific to urban outbreaks.....	22
Risk classification of countries.....	23
Part 4: EYE goal and strategic objectives.....	31
Strategic objective 1: Protect at-risk populations	31
Action 1: Where risk is high, vaccinate everyone.....	31
Action 2: Vaccinate every child	35
Action 3: Risk assessments	38
Strategic objective 2: Prevent international spread	38
Action 1: Protect high-risk workers	38
Action 2: Apply the International Health Regulations	39
Action 3: Build resilient urban centres	39
Strategic objective 3: Contain outbreaks rapidly	40
Action 1: Early detection. Strengthen surveillance and laboratory capacity.....	41
1. Strengthen rapid detection capacity	42
2. Increase diagnostic capacity.....	43
Action 2: Ensure emergency stockpile vaccines	43
Action 3: Rapid outbreak response	46
Part 5: Keys to success	48
1. Availability of accessible, affordable vaccines and a sustained vaccine market	48

Production capacity.....	48
Reliable production	49
Global supply outlook 2017–2026.....	49
2. Political commitment and sustainable national and regional YF control strategies	50
3. Governance and partnerships	51
4. Acceleration of research and development for new tools and better practices.....	52
Part 6: Monitoring and evaluation	53
Key milestones	53
Key indicators	54
Regular updates	55
Assessing risk and setting priorities.....	55
Learning as we go	55

Part 1: Introduction and context

In 2016, two linked urban yellow fever (YF) outbreaks – in Luanda (Angola) and Kinshasa (Democratic Republic of the Congo; DRC), with wider international exportation from Angola to other countries, including China – have shown that YF poses a serious global threat requiring new strategic thinking.

The world has largely forgotten the threat posed by YF, but little more than a century ago it was a source of terror, decimating the populations of cities, destroying economies and driving political choices. Extensive, repeated epidemics in North American and European port cities during the 18th and 19th centuries spread panic, shutting down the cities and killing hundreds of thousands of people, not just from the disease but also from its economic and other impacts, such as starvation. An estimated 150 000 people died during epidemics in the United States alone, with the then capital Philadelphia losing 10% of its population in the 1793 outbreak, during which the American President, George Washington, fled the city with his government.

The major leaps in biomedical research at the end of the 19th century led to identification of mosquitoes as the source of YF transmission and experiments to identify the infective agent. With the newly opened Panama Canal markedly increasing population movements through YF endemic territory, the Rockefeller Foundation's International Health Commission decided to set up teams to investigate YF eradication, first in South America, then later in Africa. This led to isolation of the YF virus strain in 1927, which in turn led to development of two vaccines, one grown in mouse brain (the "French neurotropic vaccine"; FNV) and later, by the Rockefeller team, the live attenuated 17D vaccine – a version of the safe, highly efficient vaccine still used today, requiring only one shot to confer lifelong immunity and excellent cost–benefit ratios.

The French neurotropic YF vaccine was a good mass campaign vaccine because it was administered by scarification, permitting vaccination of up to 800 people per hour, or about 5000 per day. By 1953, 56 million Africans had been vaccinated. This led to a dramatic drop in cases in the francophone countries of Africa where vaccination was performed, whereas the disease remained epidemic in neighbouring anglophone countries that did not practice vaccination, providing evidence that an effective vaccination strategy can achieve elimination of epidemics. However, the FNV caused some severe neurological adverse effects, which led to discontinuation of its use (production ceased in 1983), including its use in mass campaigns in Africa.

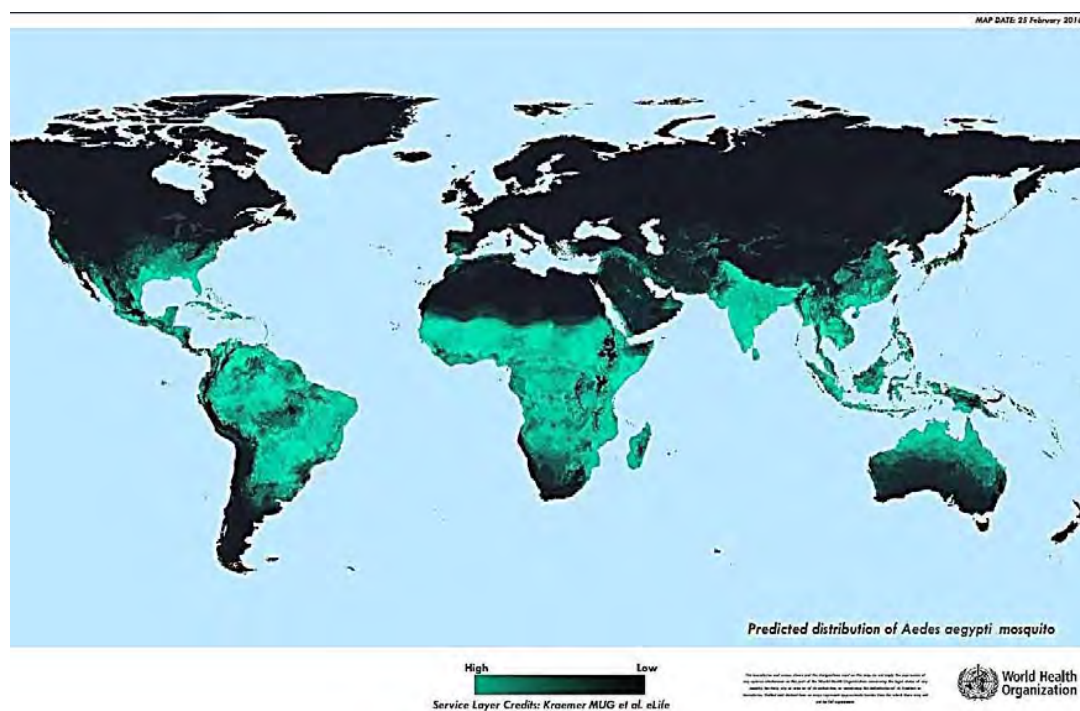
In the early 2000s, an increase in outbreaks in West Africa, with clusters of cases reported in urban settings, led to the launch of the YF Initiative, supported by Gavi, to reduce the risk of urban epidemics. This three-pronged strategy, which began in 2005, included the introduction of the YF vaccine into routine child immunization programmes in endemic countries, mass preventive campaigns in at-risk areas, and the setting up of a global vaccine stockpile to permit rapid emergency mass campaigns in response to outbreaks. This led to vaccination of 114 million people and has prevented epidemics in West Africa since 2010. However, reduction of risk in West Africa did not alter risk in central and eastern African countries, where most recent outbreaks have occurred. A modelling study based on African data sources estimated that the burden of YF during 2013 was 84 000–170 000 severe cases and 29 000–60 000 deaths (Garske T. et al. Yellow fever in

Africa: Estimating the burden of disease and impact of mass vaccination from outbreak and serological data. PLoS Med. 2014;11(5):e1001638).

Changes in outbreak drivers – urbanization and peri-urbanization, ease and speed of population movements, changes in work (e.g. mining and construction), with large numbers of workers being recruited internationally (e.g. Chinese workers in Angola) – have led to large urban outbreaks with international spread. Ebola has already demonstrated graphically what happens when a pathogen – even one not very transmissible – gets into a crowded, mobile, urban population. The West African Ebola outbreak of 2014–2015 began in a remote area but when it arrived in urban areas it spread explosively and was transported internationally.

These are just warnings of much bigger outbreaks to come – including the potential for Asian outbreaks in countries such as India and China, which harbour *Aedes* mosquitoes and are home to 2 billion people who are immunologically naïve for YF (Figure 1).

Figure 1. Probability of occurrence of the *Aedes aegypti* mosquito under current environmental and land cover conditions



Lessons learnt from recent YF control programmes

Following the early success of the YF investment case, the Gavi Board endorsed additional support for African countries at medium risk of YF outbreaks in December 2013, using a vaccine investment strategy (VIS) process. This was intended to complement mass preventive campaigns and routine

immunization. However, countries have been slow to apply to Gavi for support. Furthermore, in many countries vaccine coverage has stagnated.

Routine immunization: obstacles to progress

Vaccine supplies: A major block to progress has been the limited vaccine supply. Between 2013 and 2015, 15 countries among the 34 that introduced the YF vaccine into their routine immunization programmes reported a YF vaccine stock-out at national level, with consequences for national coverage. The problem is chronic (Table 1).

Table 1. YF vaccine stock-outs in Africa and in Latin America and the Caribbean, 2013–2015

	Number of countries reporting a YF vaccine stock-out at national level	
	Africa	Latin America and the Caribbean
2013	5	4
2014	7	0
2015	6	3

In Latin America and the Caribbean (LAC), all 13 countries considered at risk for yellow fever have routine YF immunization for children aged one year. Vaccine coverage is around 70%. This coverage has been negatively affected by the current global vaccine shortage. Countries receive around 50% of their estimated vaccine requirements (XXIV Meeting of the Technical Advisory Group on Vaccine-preventable Diseases, 13 May 2016, Washington, DC, United States).

To achieve effective YF control, demand and supply must match. Efforts need to be made on both sides. Upstream, manufacturers need to continue ongoing efforts to increase overall production but at the same time, a long-term consistency of demand must be achieved and commitment on number of doses and prices must be obtained. Successive YF vaccine roadmap efforts have not provided enough security to the manufacturers to justify investment and scaling up of production.

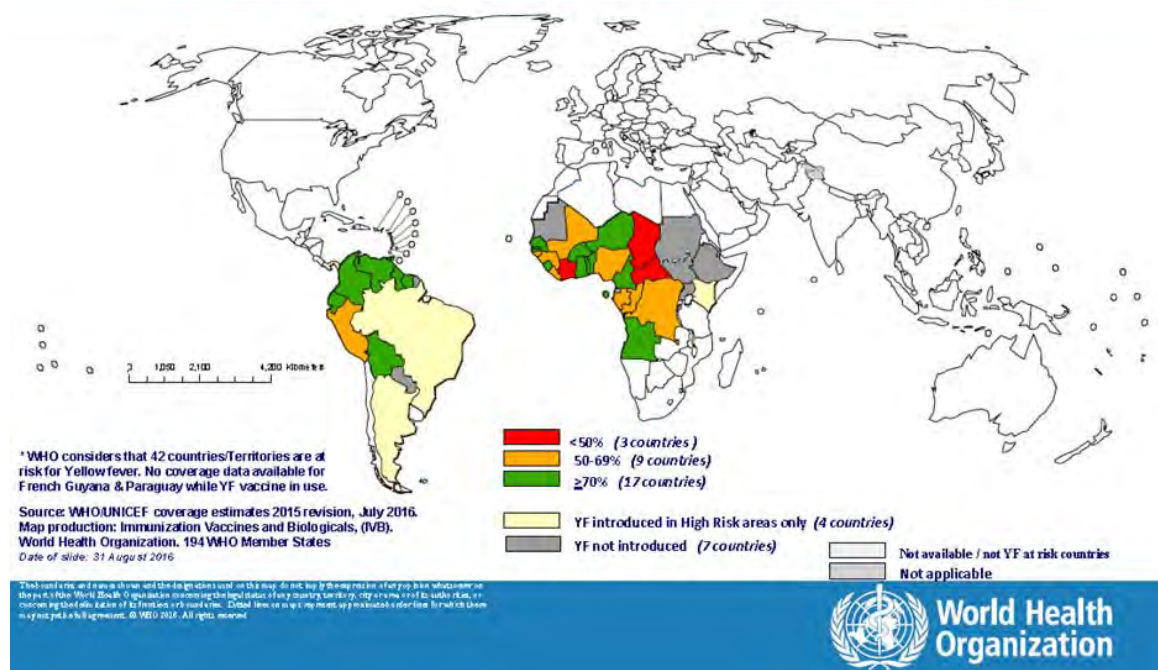
Regional and country buy-in: Due to competing vaccine introduction priorities and limited political will, no new countries have introduced the YF vaccine into their national routine immunization programmes since 2008. The level of YF risk has not been strongly communicated. The absence of a regional goal and well-communicated strategy has left countries without direction on this issue. Regional and national technical advisory groups (TAGs) have a critical role in supporting countries to introduce the yellow fever vaccine into their routine programmes.

Implementation issues: In addition to supply insecurity, reasons cited for low vaccine coverage include weak vaccine management, inadequate or overly rigid vaccination practices, such as no vaccination given after 11 months, and unwillingness to open a 10 or 20 dose vial for one child only. Vaccine supply priority is always given to outbreak response.

As a result of these obstacles, childhood immunization coverage is too low to maintain sufficient immunity (Figure 2). Specific reasons for low coverage need to be analysed, addressed and monitored. Differences between measles and YF vaccine coverage (both given at nine months in Africa) also need to be monitored and reasons better understood. In 2015, the median coverage in 22 African countries with both vaccines in national routine immunization programmes was 75% for

the first dose of measles and 70% for YF (Source: WHO/UNICEF Estimates of National Immunization Coverage; WUENIC). Countries reporting a significant difference between the two vaccines also reported a major stock-out of YF vaccine.

Figure 2. Immunization coverage with YF vaccine in infants in at-risk countries, 2015



The global emergency stockpile: Since 2004, the global emergency vaccine stockpile managed by the International Coordinating Group (ICG) for vaccine provision and funded by Gavi is at the level of 6 million doses. Until the epidemic in Angola and DRC, 6 million doses had been sufficient to control YF outbreaks in a one-year period. Only once had the 6 million doses been used (in 2008, to control an outbreak in Brazil and Paraguay). In 2016, the YF emergency stockpile has been replenished twice, bringing it up to 18 million doses. Gavi made an exceptional decision to cover the costs of stock replenishment, and therefore in 2016 the ICG stockpile financed by Gavi was 12 million doses out of the 18 million. Other contributors were the Central Emergency Response Fund, Bio-Manguinhos, the Government of Angola and the ICG revolving fund.

The rapid replenishment and increase of the stockpile has been possible thanks to excellent coordination and collaboration among vaccine manufacturers (reprioritizing their production plans) and the WHO–UNICEF working group, which has worked with affected countries to reprogram Expanded Programme on Immunization (EPI) vaccine routine shipments and thus avoid country stock-outs, while at the same time maintaining 6 million doses in the stockpile, and finally to Gavi who has provided critical financial support for these exceptional requests.

In the future, a plan will be required for rapid scale up of production if demand exceeds the vaccine stocks.

Programme governance: The longer term oversight of the YF initiative was provided to some degree by the YF partnership, made up of key public health partners around the world. The main focus of the group was to assist in the implementation of the preventive mass vaccination campaign, improve adverse event following immunization surveillance within countries conducting the campaign, and discuss YF virus disease activity and need for reactive campaigns. However, the group lack the appropriate authority and infrastructure to address some of the key deficiencies in surveillance, laboratory capacity and case management and to address countries hesitancies to engage in activities to improve their YF vaccination coverage. Although partners within the group often worked together to address gaps (e.g., development of YF risk assessment protocol), the group lacked the ability to systematic identify and address research gaps. A strong, participative governance will be key to the success of the strategy for eliminating YF epidemics.

A global problem: The control programme needs to be global, not only because the risk has gone beyond the classical risk borders but also because the supply issue needs to be addressed globally, for example by supporting Gavi-eligible countries in South America in the VIS. All countries need to be included in the global vision and provided with support, including by having access to the emergency stockpile, which should not be limited to Gavi-eligible countries only.

Current implementation of vaccination in Africa and LAC

LAC countries follow the recommendations of the regional TAG to control YF in the region, which include the introduction of the YF vaccine into national immunization programmes for children aged one year in every country with endemic areas (Table 2).

Table 2. Introduction of YF Vaccine into the routine EPI schedule in at-risk countries/territories in LAC, 2016

Country/territory	Year of introduction into routine EPI	Geographical area	WHO/UNICEF estimates of national immunization coverage, 2015
Panama	1974	Enzootic areas	60%
Trinidad and Tobago	1980	Nationwide	91%
Brazil	1994	Enzootic Areas	99%
Ecuador	2009	Nationwide	78%
Guyana	2000	Nationwide	99%
Venezuela (Bolivarian Republic of)	2000	Nationwide	85%
Peru	2001	Nationwide	67%
Paraguay	2006	Nationwide	71%
Colombia	2002	Nationwide	54%
Argentina	2008	Border with Brazil, Bolivia (Plurinational State of) and Paraguay	60%
Bolivia (Plurinational State of)	2003	Nationwide	88%
Suriname	2005	Nationwide	86%
French Guiana	NA	Nationwide	NA

Twenty-three countries in Africa have introduced the vaccine into routine immunization and 14 countries have conducted a preventive mass vaccination campaign (PMVC) since the beginning of the YF Initiative (Table 3).

Table 3. Implementation of vaccination in Africa, 2016

	Country	Year of introduction into routine EPI	PMVC year(s)	PMVC admin coverage (%)	PMVC survey coverage (%)	WHO/UNICEF estimates of national immunization coverage, 2015
1	Angola	1999	-	-	-	72%
2	Benin	2002	2009	99.8	90.6	79%
3	Burkina Faso	1987	2006	100.2	-	88%
4	Burundi	-	-	-	-	-
5	Cameroon	2004	2009, 2014	100.5, 94.0	89, NA	77%
6	Central African	2000	2010, 2011	90	94.3	45%
7	Chad	1985	-	-	-	84%
8	Congo	2004	-	-	-	80%
9	Côte d'Ivoire	1987	2011, 2012	97.5, NA	90.7, 91.0	58%
10	DRC	2004	-	-	-	88%
11	Equatorial Guinea	2016	-	-	-	-
12	Eritrea	-	-	-	-	-
13	Ethiopia	-	-	-	-	-
14	Gabon	2003	1995	-	-	68%
15	Gambia	1979	1979	-	-	97%
16	Ghana	1992	2011, 2012	98.7, 90.4	73.5, 84.0	88%
17	Guinea	2002	2010	96	89	60%
18	Guinea-Bissau	2008	-	-	-	90%
19	Kenya	2001	-	-	-	20%
20	Liberia	2001	2009	99.3	95.2	56%
21	Mali	1992	2006	98.7	83.3	84%
22	Mauritania	-	-	-	-	-
23	Niger	2005	-	-	-	89%
24	Nigeria	2004	2013	104	76.8	71%
25	Rwanda	-	-	-	-	-
26	Sao Tome and Principe	2003	-	-	-	93%
27	Senegal	1987	2007	99.3	94.2	80%
28	Sierra Leone	2002	2009	96.4, 98.4	94.3, NA	78%
29	Somalia	-	-	-	-	-
30	South Sudan	-	-	-	-	-
31	Sudan	-	2014, 2015	95, 93	NA, 92.8	-
32	Tanzania (United	-	-	-	-	-
33	Togo	1992	2007	98.4	96.8	85%
34	Uganda	-	-	-	-	-
35	Zambia					-

NA = Not available.

Part 2: Public health tools for YF prevention and control

There are several measures that are integral to a long-term strategy aimed at eliminating outbreaks of YF, including surveillance and laboratory testing, vector surveillance and control and vaccination.

1. YF disease surveillance

Sustained YF control strategies must rely on strong surveillance and diagnostic capacities to allow for early detection of outbreaks and rapid implementation of control measures that can help **mitigate the risk of spread and the use of extensive resources**. The recent Angola epidemic highlighted how limited surveillance and laboratory capacity worsen both the epidemic **burden** and spread: by delaying the detection of YF cases and clusters, the outbreak grew uncontained, reached a magnitude that required very resource-intensive containment measures and spread internationally by land and air through unimmunized travellers (workers). Strong surveillance and diagnostic capacity also enable an understanding of where the risk of YF is and to inform the allocation of appropriate resources. Surveillance informs targeting and intervention priorities by providing information on the evolving risk and the impact of preventive and control measures. On the other hand, in the case of YF, insufficient surveillance participated to the limited evidence of risk and lack of interest in controlling the disease.

Appropriate surveillance approaches for YF differ based on the level of risk of urban YF outbreaks, ranging from case- based, sentinel approaches to integrated disease surveillance and response (IDSR) approaches.

The **Integrated Disease Surveillance and Response (IDSR)** program is a population-based surveillance approach using aggregated data counts to compute the incidence of YF cases (suspected, probable and confirmed) at a given level (most often, district), with epidemic investigation and containment measures launched accordingly. In all countries, the IDSR framework can serve as foundation for YF surveillance.

In **case based surveillance**, a standard case definition is used to identify suspected cases, then individual information is collected and each case is sampled for confirmatory testing. Suspected cases are thoroughly documented at the individual level from the epidemiological (incl. vaccination status) and laboratory standpoints. The term “case” implies a focus on “case-level” information, rather than being an antonym to “population-based” surveillance. It can be conducted in a context of population-based surveillance; that is, involving a defined population with a denominator from which cases come and rates can be calculated.

A **sentinel** surveillance approach is a practical and efficient choice, limiting pressure on resources while achieving adequate capacity. The sentinel approach can be location based (i.e. district) or facility based (i.e. hospital); alternatively, it could target a specific part of the population, such as at risk groups (e.g. facilities taking care of high risk workers, or on mining sites). Sentinel surveillance uses data systematically collected in multiple high-quality sites across the country. Ideally, these sites are purposely selected to bring valuable information and answer specific epidemiological questions (e.g., YF virus circulation). The quality of sentinel surveillance is highly dependent on the selection of the sentinel sites. By nature, a sentinel approach cannot answer all the epidemiological

questions associated with YF; however, it is possible to combine different strategies to reach a satisfying level of information and meet the surveillance goals set. In particular, neither the burden of the disease nor the incidence trends of the disease at country level can be reflected. Consequently, whenever a case-based sentinel strategy is implemented, IDSR should still be applied as a basis for this approach, to ensure these information gaps are filled.

2. Vector surveillance and control

Both vector surveillance and control are components of the prevention and control of vector borne diseases, especially for transmission control in epidemic situations. For YF, vector surveillance targeting *Aedes aegypti* and other *Aedes* species will help inform where there is a risk of an urban outbreak. By understanding the distribution of these mosquitoes within a country can allow a country to prioritize areas to strengthen their human disease surveillance and testing and consider vector control activities.

There is currently a limited public health arsenal of safe, efficient and cost-effective insecticides. This is mainly due to the resistance of major vectors to common insecticides and the withdrawal or abandonment of certain pesticides for reasons of safety or the high cost of re-registration.¹

Sylvatic vector control is not feasible and urban vector control has proved challenging. As currently implemented, it has been unable to prevent epidemic dengue, chikungunya and Zika.

Routine vector control

Large-scale attempts to control mosquito populations and breeding sites conducted in the Americas in the 1970s were short-lived due to a combination of factors, such as diminishing awareness and political interest leading to reduced funding, dismantlement of infrastructure, and fewer vector control specialists being trained and deployed; resistance to insecticides, notably reducing the vector control arsenal; and accelerating population growth, rapid unplanned urbanization, and changes in patterns of land use, which made environments even more hospitable for flourishing *Aedes aegypti* populations.²

Routine vector control has limited efficiency, and options belong to the areas of long-term development (community engagement to control mosquito breeding sites) or research (genetically modified mosquitoes, requiring further field trials and risk assessment).

Epidemic vector control

The main contribution of vector control in the arsenal of public health measures to control YF epidemics in urban centres where transmission is occurring readily between mosquitoes, namely *Aedes aegypti*, and humans. Control efforts need to target both mosquito **larvae and adults**. Epidemic vector control should be implemented as quickly as possible in neighbourhoods and districts where YF cases live.

¹ <http://www.who.int/whopes/questions/en/>

² <http://www.who.int/emergencies/zika-virus/articles/mosquito-control/en/>

3. Vaccination against YF

There has been an effective and safe vaccine available to prevent YF since the 1930s. One dose of the vaccine provides lifelong immunity. The YF vaccine is relatively cheap, costing an average of US\$ 1.07 per dose in 2016, in 5- and 10-dose presentations.¹

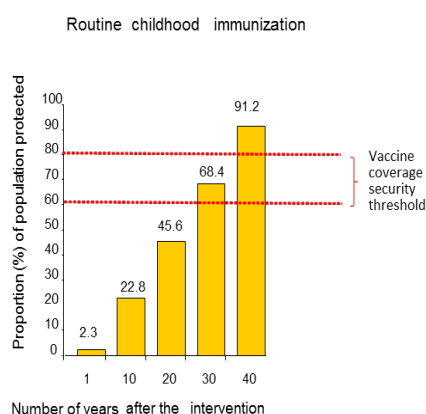
Vaccine coverages greater than 80%, with a 60-80% security threshold, are necessary to interrupt autochthonous transmission (human-mosquito-human) of YF virus within a community and ensure that sporadic unvaccinated cases do not generate secondary cases.

There are several potential ways to improve vaccination coverage in at-risk areas but each of these has potential obstacles and different costs.

3.1. Approach 1: Implementing and strengthening coverage rates of childhood YF vaccination

YF vaccine can be integrated into national routine immunization schedules and delivered through EPI in an integrated approach with other vaccines. Infant YF routine immunization is administered at nine months in Africa and 12 months in LAC, jointly with the first dose of measles-containing vaccines, at low operational costs.

Box 1: Population protected by routine childhood immunization



When well implemented by strong health systems, YF routine immunization in the EPI can provide sufficient population immunity. However, it **takes about 30 years** to build the population immunity to adequate levels to potentially stop large scale outbreaks. Once high level population immunity is established, the continued routine vaccination of new birth cohorts is a **sustainable long-term** approach to maintaining high levels of population immunity. If recently or insufficiently implemented, routine immunization alone does not represent a safe approach to controlling the risk of YF epidemics, as recently demonstrated in **Angola**.

Angola has implemented YF routine immunization since 1999. Between 2004 and 2015, WHO and UNICEF estimated that national vaccination coverages for YF ranged from 40% to 72%, with a 57%

¹ http://www.unicef.org/supply/files/Yellow_Fever.pdf

average.¹ No preventive mass campaign has been conducted. At the time of the 2016 epidemic crisis, with international spread, the average population immunity against YF was very low among the 25 million people living in the country.

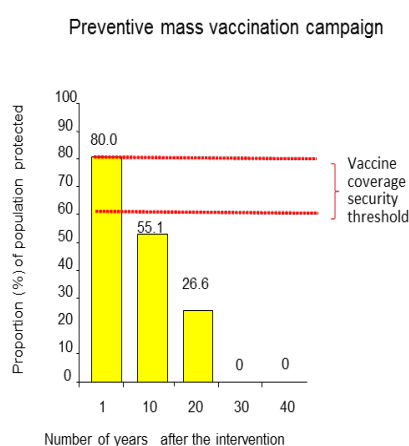
Current patterns of population movements, with frequent exchanges between sylvatic and rural areas, are such that subnational approaches to risk control might not be adequate in all countries specifically if vaccination of travellers within a country is suboptimal. In these countries, a national approach might be more appropriate in a comprehensive risk mitigation strategy

3.2. Approach 2: Conducting preventive mass vaccination campaigns

PMVCs are **the most efficient** approach to **rapidly increasing population immunity** levels in high-risk areas and controlling the risk of YF epidemics on a **short-term** basis, but the protection provided wanes rapidly, becoming inexistent after 25 to 30 years.

Preventive mass campaigns target the at-risk population older than nine months. They have low wastage rates of around 10%. These one-time transversal campaigns are associated with operational costs of approximately US\$ 0.65 per dose delivered. They are fairly resource-intensive and require strong commitment at all levels (political to community) and intense coordination between partners. By actively seeking to reach everyone and attaining high vaccine coverages, preventive mass campaigns participate in strengthening **health equity**. Most countries are used to campaign implementation and usually reach high coverages (>90%; see Table 3). However logistic challenges remain, particularly regarding waste management and monitoring of adverse effects following immunization. The capacity of a system to overcome these challenges directly affects the quality of a mass campaign.

Box 2: Population protected by preventive mass campaigns



Current patterns of population movements, with frequent exchanges between sylvatic and rural areas, are such that subnational approaches to risk control do not seem reasonable and only national approaches provide comprehensive risk mitigation. The situation of Cameroon illustrates the importance of planning **nationwide** rather than subnational mass campaigns in countries

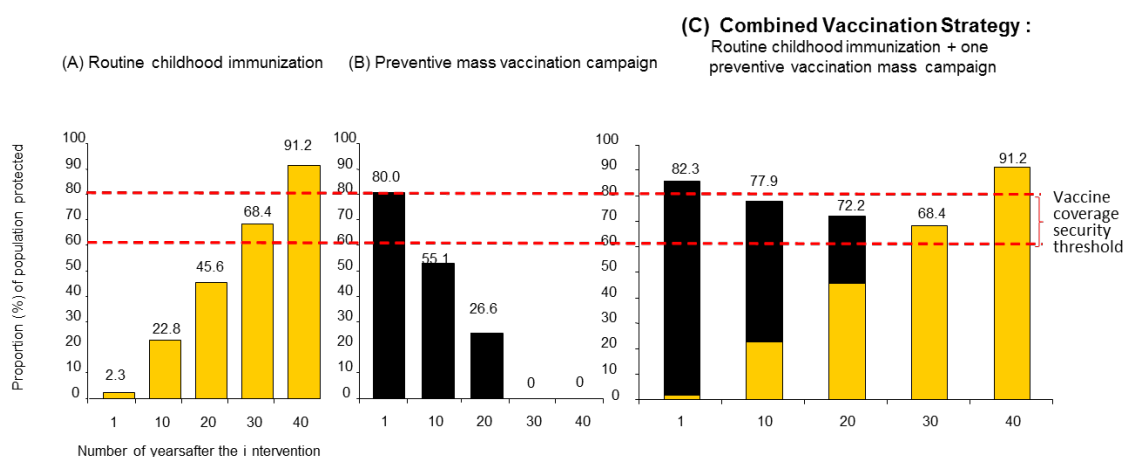
¹ http://www.who.int/immunization/monitoring_surveillance/data/ago.pdf

deemed at risk. In 2009, subnational preventive mass campaigns were mounted in a “patched approach” that protected only the districts at highest risk. In 2011, a YF outbreak hit unimmunized areas located between district “patches” where preventive mass campaigns had been conducted. The “patched approach” ultimately caused greater morbidity and required more resources and coordination to address the consequences than if a comprehensive plan had been formulated in the first place.

An optimal, sustained public health impact can be achieved when PMVCs are combined with routine immunization. **Combined vaccination strategies** are estimated to have reduced the burden of YF by more than half in countries at highest risk for YF epidemics – by up to 92% in some areas – and averted almost half a million YF cases.

Large-scale vaccination campaigns conducted in West Africa from the 1940s to the 1960s were successful by themselves in eliminating the risk of YF epidemics from the region; but in the absence of associated routine immunization or catch-up campaigns, YF epidemics resurged in the 1980s due to low vaccination coverages. Most recently, vaccination strategies combining preventive mass vaccination campaigns and routine immunization were successful at eliminating the risk of YF epidemics on a long-term basis. More than 150 million individuals were protected against YF between 2007 and 2015 in the 13 countries at highest risk for YF in Africa. No YF epidemic has been recorded in those countries.

Box 3: Population protected by combined vaccination strategy



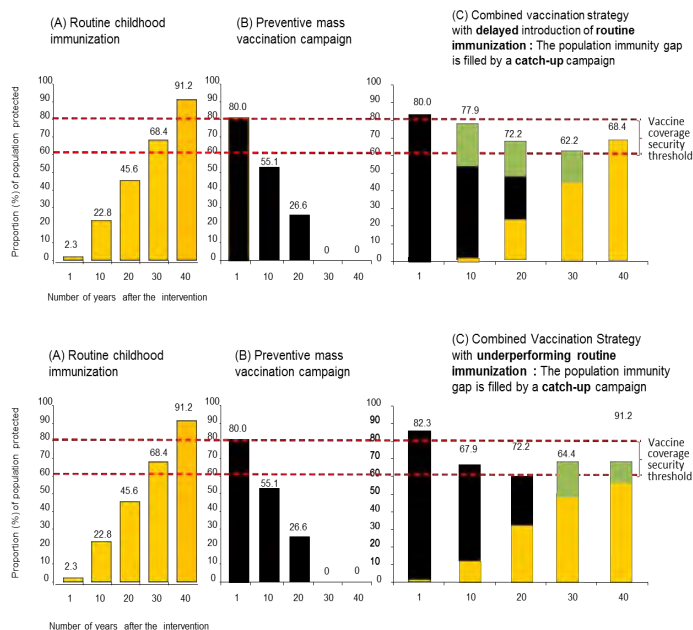
3.3. Approach 3: Implementing catch-up campaigns

Where low routine vaccination coverage and potential dilution of preventive vaccine campaign vaccine coverage due to population movements, mounting targeted “catch-up campaigns” would enable reaching under-vaccinated cohorts or pockets. These may target age-specific vaccination gaps, or geographic areas where population immunity is low.

Catch-up campaigns are a reasonable **risk mitigation** measure in high-risk areas to **close immunization gaps**. They are resource-intensive, particularly as vaccination coverage surveys might need to be performed to determine areas with low coverage, and require the same amount of coordination and fixed costs as large-scale preventive mass campaigns. Catch-up campaigns are **not**

a **substitute** to well-functioning routine immunization systems. Countries should be engaged though to perform periodic assessments of their vaccination coverage in areas at risk for outbreaks of disease in order to identify gaps in coverage and response proactively. Assessments could be performed at regular intervals (e.g., every 5-10 years) or in response to large population movement or other factors that might impact coverage.

Box 4: Population protected by delayed or underperforming routine childhood immunization combined to preventive mass campaigns



3.4. Approach 4: Maintaining a stockpile for reactive campaigns

A large supply of readily available YF vaccine can be kept for any future emergency response. Vaccine stockpiles enable a rapid access to a limited supply of vaccines, allowing countries to **respond to YF outbreaks** in a timely fashion. In a limited vaccine supply context, the international management of vaccine stockpiles is necessary to ensure an **equitable distribution**. Until optimal vaccination strategies are implemented to control the risk of YF and prevent epidemics, YF vaccine stockpiles will be necessary.

4. Targeting travellers and improving IHR adherence

The recent Angola epidemic highlighted how YF can spread internationally by land and air through unimmunized travellers (workers from China and DRC). In the country there are 400 000 migrant workers from DRC, at least 220 000 Portuguese, and about 260 000 Chinese (2008 estimates). In LAC, unimmunized “eco-tourists” lodging in sylvatic areas are a recognized source of introduction of YF virus into non-forested areas.

The YF immunization status of travellers needs to be confirmed upon arrival into and departure from areas at risk for YF to prevent YF exportation to immune-naïve populations where the potential for local transmission exists.

Although little data is available, the International Health Regulations (2005) (IHR) are inconsistently applied in countries at risk for YF, including upon airport arrival. As experienced during the 2015 Ebola epidemic, points-of-entry personal data and health checks are difficult. Yet lessons can be learnt from that experience that could inform a strengthening of IHR application.

The recent Angola–DRC YF epidemics also highlighted the need for uniform vaccination cards that are cheap but hard to counterfeit: viraemic unimmunized migrant workers used counterfeited cards to cross land borders and spread YF into immune-naïve populations.

No cost figures are available, but they should be fairly low compared to vaccination and surveillance activities.

In summary, YF cannot be eradicated but epidemics can be eliminated if population immunity levels are effectively raised through mass vaccination and *sustained* by routine infant immunization. Different approaches enable detection of YF and mitigation or prevention of the risk of YF epidemics. They can be used alone or in combinations, with different impacts. The appropriate (cost-effective) combinations of approaches depend on the risk level of a country.

It is important to emphasize that immunization programmes must maintain high levels of immunity, and that cessation of routine immunization will eventually lead to a return of outbreaks, as happened in Senegal in 1965, about five years after routine immunizations were stopped.

In West Africa, the three-pronged approach – including YF vaccine in routine immunization, performing mass vaccinations in at-risk countries/populations, and responding rapidly to outbreaks – has successfully controlled the disease. This three-pronged approach works and still provides the basic ingredients needed for an effective strategy. However, the change in risk both in vulnerable, fragile countries and internationally, and the resurgence of vectors, means the way in which these tactics are strategically applied needs to be scaled up and tackled globally.

This strategic document focuses on activities recommended in Africa and LAC, where the disease is endemic. Many experts worry that the disease will reach other continents, such as Asia. This risk is difficult to estimate. We assume, however, that by protecting populations in areas currently endemic for YF and by protecting travellers who could spread the disease, the risk of exportation will be contained.

The following risk-driven combination of strategic options to detect and control YF is proposed:

Table 4. Public health goal and combination of strategic options for YF detection and control by risk level

Country Risk level	Public health goal	Combination of strategic options
High	Protect at risk population Contain outbreaks rapidly Prevent international spread	<ul style="list-style-type: none"> • Three-pronged vaccination approach to maintain high population immunity levels (routine immunization, catch-up campaigns, preventive mass campaigns) • Monitoring of population immunity • Rapid response to outbreaks • Case-based surveillance and laboratory testing • Targeting travellers and improving IHR adherence (upon entry and departure) • Readiness and health systems strengthening
Moderate	Contain outbreaks in high risk areas Prevent international spread	<ul style="list-style-type: none"> • Sentinel surveillance and laboratory testing • Rapid response to outbreaks • Improving IHR adherence • Readiness and health systems strengthening
Currently not considered at risk but potential for YF transmission	Early detection of suspected cases Prevent introduction of YF	<ul style="list-style-type: none"> • Integrated surveillance and laboratory testing • Improving IHR adherence • Readiness and health systems strengthening

Part 3: Evolution of the global YF risk

Recent changes in transmission dynamics

In the latter half of the 20th century the most frequent YF virus transmission patterns were either: (1) sylvatic – where the animal reservoir (non-human primates living in the forest or jungle) – infects tree-dwelling mosquitoes which in turn bite humans who enter the forest to hunt or work; or (2) intermediate – where the mosquitoes moving between the forest and human settlements are implicated, with humans serving as the hosts in the transmission cycle. In Africa, virtually all intermediate type outbreaks have led to outbreaks involving the *Aedes aegypti* (urban) vector. This cycle can occur in rural villages and small towns, but large outbreaks have occurred when infected people from these rural settlements travelled to urban centres. More recently, however, although YF virus transmission patterns *per se* have not changed, the sequence has been increasingly short-circuited from sylvatic directly to urban, inter-human transmission. Urban outbreaks are particularly deadly and disruptive and are more likely to cause international spread. In contrast to Africa, YF cases in LAC have been nearly exclusively sylvatic, with very few small outbreaks of the urban type, although large, unvaccinated coastal populations are at potential risk. There is no recognized intermediate cycle.

Vectors: The worldwide resurgence of the primary vector responsible for urban outbreaks – *Aedes* species mosquitoes – means that globally, more cities and countries are at risk. The current global outbreak of Zika virus disease and continuing outbreaks of dengue fever and chikungunya disease, all caused by viruses primarily transmitted by *Aedes aegypti*, are indicative of the success of, and threat posed by, *Aedes aegypti*. Wherever and whenever Zika, chikungunya and dengue virus occur, this should alert countries to the possibility that YF virus could also be successfully transmitted in their communities.

Environmental risk: Deforestation, climate change, more incursions into forests and jungles for mining, construction and to clear land for agriculture are all increasing contacts between humans, the animal reservoir and the mosquitoes transmitting YF virus. Humans no longer stay at the edge of forests but move in, work there and move rapidly back to cities or large settlements (in a matter of hours), thus contributing to the potential rapid spread of YF virus. All these risk-amplifying factors – urbanization, large population movements, climate change and increasing exposure of workers to infected mosquitoes in jungles and forests (particularly those working in mining and forestry) – are driving the change in YF epidemiology.

Human risk: Movement of populations for commerce and due to civil unrest can often lead to lower population immunity, particularly in urban centres, as previously unvaccinated persons move to areas that might have benefited from vaccination campaigns earlier (e.g. Abidjan in Côte d'Ivoire experienced outbreaks several years apart with a notable decrease in population immunity between outbreaks).

Risk specific to urban outbreaks

In urban outbreaks, population density, crowding, low levels of population immunity, daily population movements in and out of, and around, the city, and conditions conducive to high vector

density such as plentiful breeding sites in and around houses, increase transmissibility, raising the risk of large-scale outbreaks.

Urban outbreaks are characterized by their rapid amplification, capacity for international spread, and impact not only on public health but also on economic, social and political life. The West African Ebola outbreak showed that when a pathogen spreads to capital cities it can amplify into a major epidemic on scale never observed before. The public health impact of such outbreaks is huge and so too are the economic losses: in the Republic of Korea, an outbreak of Middle Eastern respiratory syndrome in June 2015 caused only 185 cases but paralysed Seoul for several weeks, precipitating losses of millions of dollars in a matter of days.

Responding to outbreaks in large urban settings is challenging and costly and, in a globalized world, such outbreaks have impacts on travel and trade beyond the health consequences alone.

Risk classification of countries

While the YF virus has caused outbreaks in many countries in past decades, it is still difficult to assess the risk of re-emergence. Such re-emergence depends on a convergence of factors, requiring virus circulating in the animal reservoir, infection in mosquitoes, and transmission to humans. Many unknowns remain. In this challenging context, we reviewed the available information and applied specific criteria to classify the countries and propose preventive strategies accordingly. In a context of growing concern and perception of globalized risk, we decided to be inclusive in the number of reviewed countries.

Forty-seven countries (34 in Africa and 13 in Central and South America) are either endemic for, or have regions that are endemic for, YF¹. In addition to these 34 African countries, we added Zambia, as a working group of international experts included north-western and western provinces as areas of low exposure (Jentes ES et al. The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the Informal WHO Working Group on Geographic Risk for YF. *Lancet Infect Dis.* 2011; 11:622–32).

Africa

For Africa, we used a **three-step approach** to reclassify the 35 countries into different risk categories and propose preventive strategies accordingly.

- **Step 1.** Estimation of **crude risk** for YF transmission. Crude risk represents the likelihood for YF disease cases to occur if the population is inadequately vaccinated. Crude risk was established to identify countries that are naturally at higher risk and should be targeted to achieve sustained, high level of vaccine coverage.

¹ : Yellow fever: Fact sheet. Geneva; World Health Organization; updated May 2016;
<http://www.who.int/mediacentre/factsheets/fs100/en/>

- **Step 2.** Estimation of **actual risk** for YF disease cases and urban outbreaks. Among countries determined to have a high crude risk of YF virus transmission, their population immunity was assessed to further highlight which countries are most at risk for outbreaks.
- **Step 3.** prioritization of countries based on their perceived level of risk. The prioritization is meant to guide further implementation of preventive activities.

Step 1. Crude risk estimation

The crude risk for YF virus transmission in a country was estimated based several key factors:

- (1) Timing and intensity of YF virus circulation in the country.
 - Assessed using both direct evidence of YF circulation (i.e., serosurveys in vaccination-naïve populations) and proxies for current (recent reports of YF cases) and historical active YF virus circulation and human disease cases; we used mass immunization campaigns in the 1940s–1960s as a proxy for intense virus circulation. We used the following definitions and cut-offs:
 - number of reported YF outbreaks in the last 25 years
 - serosurvey from the recent comprehensive risk assessments – see Table 3 – demonstrating YF-virus specific neutralizing antibodies prevalence >3% in at least one zone¹
 - presence of YF cases reported between and 2011–2016
 - national mass immunization campaign prior to the Yellow Fever Initiative.

Any country positive for one of these criteria was initially classified as being at high risk (Table 5). This analysis enabled identification of **27 “high-risk”** and **eight “moderate-risk”** countries.

- (2) Estimate of the transmission potential in terms of the basic reproduction number
 - A working group from Imperial College, London, developed a model to assess the geographically varying transmission potential and resulting disease burden of YF in the endemic zone in Africa. They considered a wide range of environmental factors as potential covariates, with the final (best-fitting) model including population size, longitude, the enhanced vegetation index and land cover type. The model was used to estimate the transmission potential in terms of the basic reproduction number, R_0 . The R_0 model was fitted to outbreak data between 1984 and 2013.

The R_0 were used to verify if the categorization of countries based on the timing and intensity of YF virus circulation in the country (see point 1 above) needed to be adapted. We used a cut-off point for $R_0 \geq 1.25$, being the median (P50) value of the R_0 distribution.

¹ Risk assessment on yellow fever virus circulation in endemic countries, available from http://apps.who.int/iris/bitstream/10665/112751/1/WHO_HSE_PED_CED_2014.2_eng.pdf

Table 5. Risk of YF virus circulation of 35 African countries

	Country	Numbers of YF outbreaks 1990–2016	Recent report of YF cases ¹	National PMVC prior to the YFI	High seroprevalence ²	Ro≥1.25	Risk level
1	Angola	1	Y				High
2	Benin			Y		Y	High
3	Burkina Faso	5		Y		Y	High
4	Cameroon	5	Y	Y			High
5	C. A. R.	3				Y	High
6	Chad	1	Y	Y			High
7	Congo	2	Y			Y	High
8	Côte d'Ivoire	7	Y	Y		Y	High
9	DRC	4	Y		Y		High
10	Eq. Guinea		Y				High
11	Ethiopia	1	Y		N		High
12	Gabon		Y ³	Y		Y	High
13	Gambia			Y		Y	High
14	Ghana	1	Y			Y	High
15	Guinea	10		Y		Y	High
16	Guinea-Bissau		Y ⁴			Y	High
17	Kenya	2			N		High
18	Liberia	5		Y		Y	High
19	Mali	2				Y	High
20	Niger					Y	High
21	Nigeria	3				Y	High
22	Senegal	5	Y	Y		Y	High
23	Sudan	4	Y		Y ⁵		High
24	South Sudan	1			Y ⁶		High
25	Sierra Leone	3				Y	High
26	Togo			Y		Y	High
27	Uganda	2	Y		Y		High
1	Burundi					N	Moderate
2	Eritrea					N	Moderate
3	Mauritania					N	Moderate
4	Rwanda				N	N	Moderate
5	Sao Tome and P.					NA	Moderate
6	Somalia					N	Moderate
7	Tanzania (United Republic of)					N	Moderate
8	Zambia				N	N	Moderate

Ro = basic reproductive number; PMVC = preventive mass vaccination campaign; YFI = Yellow fever Initiative; Y = yes; N = no; NA = not available.

- In Ethiopia, the YF risk assessment found evidence of risk and virus circulation limited to the south-western part of the country. South-western Ethiopia only is therefore considered to be at high risk.

- PMVCs conducted in the 1940s–1960s, except for Gabon and the Gambia, which conducted national mass campaigns in response to epidemics in 1995 and 1979, respectively.

¹ 2011–2016.

² Serosurvey demonstrating neutralizing antibody prevalence >3% in at least one zone (multidisciplinary risk assessment).

³ Cases were recently laboratory confirmed.

⁴ Imported cases were recently confirmed (area of origin unclear).

⁵ In Sudan, the national average was 5.1%, ranging from 2.1–7.3%.

⁶ In South Sudan, the national average was 7.2%, ranging from 4.5 to 8.6%.

- (3) Assessment of urban outbreak risk based on reports of recent or current outbreaks of *Aedes aegypti*-transmitted viral diseases

Recent or current outbreaks of dengue fever, Zika virus disease, and chikungunya were assessed in the 35 countries in Africa and 13 countries in Americas where YF is considered endemic. In addition, these criteria were also applied to countries in Africa that neighbour areas with risk of YF and outbreaks to define “**potential for YF virus transmission**” (Figure 3).

- (4) Determination of countries with no risk of YF virus circulation and limited potential for outbreaks of disease

Last group of countries were limited to those who had no risk of YF virus circulation and also reported no evidence of arbovirus circulation (e.g., dengue, chikungunya, or Zika virus disease cases) (Figure 3). Although countries are generally felt not to be significant risk for outbreaks of YF disease, several of these countries could be at risk for a sustained urban outbreak of YF given the predicted distribution of the *Aedes aegypti* mosquito.

Figure 3. Risk of YF outbreaks in Africa by country, 2016



Step 2. Actual risk estimation to inform immunization activities

Based on the crude risk of YF virus circulation, we then assessed countries by the current proportion of the population that is likely protected against YF to determine the actual risk of YF disease and outbreaks. We used vaccine-acquired population immunity, as calculated by the working group from Imperial College, London, in 2016 and focused on the 27 high risk countries based on YF virus transmission patterns (i.e., crude risk). Population immunity is the proportion of individuals protected against YF in a given population (non-susceptible). In each country, population immunity was calculated at district level from cumulative data on preventive mass campaigns, routine immunization, outbreak response and catch-up campaigns. The computation accounted for target population, vaccine coverage and the year of the respective activity. District-level coverages were averaged across each country to provide a national estimate.

Among the high-risk countries, a number have already conducted immunization activities and show a higher population immunity (Table 6).

Table 6. Vaccine-acquired population immunity for high-risk countries, Africa 2016

	Country	Pop. immunity
1	Côte d'Ivoire	0.9
2	Togo	0.888
3	Benin	0.884
4	Liberia	0.873
5	Burkina Faso	0.869
6	Sierra Leone	0.857
7	Central African Republic	0.839
8	Guinea	0.808
9	Mali	0.788
10	Cameroon	0.721
11	Ghana	0.720
12	Senegal	0.719
13	Gambia	0.687
14	Gabon	0.675
1	Angola	0.508
2	Sudan	0.455
3	Niger	0.354
4	Nigeria	0.337
5	Congo	0.319
6	Chad	0.314
7	DRC	0.285
8	Kenya	0.270
9	Guinea-Bissau	0.173
10	Uganda	0.017
11	South Sudan	0.015
12	Ethiopia	0.005
13	Equatorial Guinea	0

Thirteen countries show a population immunity below 60%, indicating that herd immunity is not sufficient to prevent outbreaks. These countries need large-scale preventive approaches. Two countries, Gabon and the Gambia, lie between 60% and 70% and should consider methods to improve their vaccination coverage to prevent outbreaks of disease.

Ghana is a special case: PMVCs were conducted in 2011 and 2012 (two phases) but large areas of the country were not covered; the approach was “patched”, as described above. It is therefore recommended that the campaigns be completed and full coverage achieved in remaining districts.

Step 3. Prioritization among the countries perceived to have the high risk of outbreaks given YF virus circulation and low vaccine immunity

The prioritization exercise was completed (Table 7), based on:

- History of arbovirus outbreaks: History of arthropod-borne virus (arbovirus) outbreaks also transmitted by Aedes species (dengue, Zika, chikungunya). Presence of dengue was given 1–3 grading points based on the quality of documentation. Presence of chikungunya and Zika virus was graded with one point each. A grading of 0 denotes absence of all documented arboviruses.
- Expert opinion. Based on experience and practical considerations, subject matter experts provided input on the prioritization. Some of their considerations are included below:
 - o Nigeria is the only one of the 12 countries originally approved by Gavi under the YF investment case which has not yet finalized its national PMVC. Nigeria was affected by one of the largest YF epidemics in the last 35 years, with the estimated number of cases being greater than 116 000, with 24 000 deaths. It remains a major gap in West Africa and was identified as a top priority by the experts.
 - o Ghana and Sudan also need to ensure that the whole country is covered – to complement the 2011–2012 campaign in Ghana and phase 2 in Sudan.
 - o Angola and DRC also need ensure that the whole country is covered after various campaigns organized in 2016 in response to the outbreaks.
 - o Uganda had YF outbreaks in 2010 and 2016 affecting three areas in distinct locations of their country and have minimal to no population immunity except in the areas targeted by the reactive campaigns
 - o Ethiopia had a sizeable outbreak in 2013.
 - o Guinea-Bissau remains an unprotected space in West Africa.
 - o For the remaining countries, the difference is small, but a slightly higher priority was given to Congo and Equatorial Guinea because of the reporting of recent cases in neighbouring countries.

Table 7. Proposed priority for African countries at high risk of YF

	Country	History of arbovirus outbreaks	Expert opinion
1	Nigeria	5	Complete investment case – West Africa Gavi approved
2	Ghana	3	Complete investment case – West Africa Gavi approved
3	Sudan	4	Last phase – finish campaign Gavi approved Recent outbreak
4	Uganda	4	Recent outbreaks Commitment to introduction into routine EPI
5	DRC	4	Recent outbreak response – country to be finalized
6	Angola	3	Recent outbreak response – country to be finalized
7	Guinea-Bissau	4	West Africa higher risk
8	Ethiopia	3	Recent outbreak
9	South Sudan	3	Recent outbreak
10	Congo	2	Recent confirmation of cases
11	Eq. Guinea	2	Recent confirmation of cases
12	Chad	2	
13	Niger	1	

This ranking should be considered preliminary as it has to be discussed with the respective countries and at the regional level.

Latin America and the Caribbean

For **LAC**, YF continues to be a significant public health problem for the 13 countries with endemic areas, and all are considered to be at high risk. Over the last 30 years, YF virus activity has been restricted to the enzootic area shared by the Plurinational State of Bolivia, Brazil, Colombia, Ecuador, French Guyana, Guyana, Panama, Peru, Suriname, Trinidad and Tobago, and the Bolivarian Republic of Venezuela.

Since late 2007, the region has experienced intense circulation of the YF virus with extensive epizootics and outbreaks of human cases. In 2008, cases of YF were reported in the metropolitan area of Asuncion, Paraguay. Prior to this, the last confirmed urban outbreak of YF in LAC had occurred in 1942 in Brazil. This event, in addition to the proliferation of *Aedes aegypti* in the Region, shows the high risk of re-urbanization that still exists in LAC. The endemic area was extended to include Paraguay and northern Argentina, because of human cases and epizootics detected in 2008.

In 2013, the regional TAG reviewed the YF problematic in countries of Latin America. The TAG reaffirmed that the strategy to control YF should include surveillance and YF vaccination through a combination of routine immunization strategies and large-scale disease-prevention campaigns. Campaigns in response to outbreaks should be conducted if vaccine coverage is inadequate in the population.

As of 2016, every country in the region with enzootic areas has added the YF vaccine to its national immunization schedule. In Argentina, Brazil and Panama, the vaccine is only administered in areas of potential risk (Table 2).

Population immunity could not be estimated for at-risk countries in LAC. However, mass preventive campaigns were usually conducted long ago and, as described earlier in this document, routine immunization has achieved suboptimal levels. Experts have estimated that most countries need to conduct mass campaigns, to be targeted at the very specific high-risk zones or according to the remaining susceptible population. Among the 13 countries with endemic areas, experts have prioritized Peru (recent outbreaks), Colombia and the Bolivarian Republic of Venezuela.

YF circulation was never identified in the Caribbean countries and territories, which are not endemic for the disease, except in Trinidad and Tobago. Yet the intense and rapid spread of both the chikungunya and Zika viruses and recurrent dengue epidemics in large, densely populated regions of South America, Central America and the Caribbean outside the enzootic zone make them countries with **“potential for YF transmission”**, on the same basis as the risk categorization proposed for Africa.

Figure 4. YF risk areas in South America, Panama, and Trinidad and Tobago



Part 4: EYE goal and strategic objectives

To respond to the increased risk of large urban outbreaks with international spread that could threaten global health security, a comprehensive long-term strategy has been developed, able to target the most vulnerable countries and regions, while addressing global risk by building resilience in urban centres and readiness in areas with potential for outbreaks, and at the same time ensuring reliable vaccine supply to predict needs and shape vaccine production.

EYE goes beyond immunization activities to address the increased risk and adapt to changing YF epidemiology. An efficient surveillance system and the control of international dissemination are essential pillars complementing population protection. This can only be achieved through strong partnerships and collaborations across agencies, disciplines and sectors.

EYE goal: To eliminate the risk of YF epidemics globally by 2026

The EYE strategy has three strategic objectives:

- 1- protect at-risk populations;
- 2- prevent international spread;
- 3- contain outbreaks rapidly.

The EYE strategy will only be successful if core activities are initiated from the very beginning to provide cross-cutting support to the three central objectives. These activities are:

- continued availability of accessible, affordable vaccines through a sustained vaccine market;
- political commitment at regional and country levels;
- robust governance and strong partnerships for EYE implementation;
- research to support better tools and practices.

Strategic objective 1: Protect at-risk populations

Action 1: Where risk is high, vaccinate everyone

Preventive mass vaccination campaigns

To rapidly reduce the risk of outbreaks, it will be important to target areas at high risk of YF virus transmission and inadequate population immunity.

Africa. As previously noted, there are 13 countries in Africa identified as high risk where PMVC would be considered to increase the inadequate levels of immunity rapidly (Figure 5): Angola, Chad, Congo, DRC, Ethiopia, Equatorial Guinea, Ghana, Guinea Bissau, Niger, Nigeria, South Sudan, Sudan, and Uganda.

While the primary goal is to build a barrier of human immunity in sylvatic areas and protect populations in the zone of emergence, the preventive strategies have to be national in scope to account for the reality of frequent and rapid population movements and to prevent urban outbreaks. The exception is Ethiopia, for which the south-western part of the country is scheduled for a PMVC as seroprevalence surveys and confirmed epidemics have indicated virus circulation in this area only.

Kenya is another special case: it is included as a high-risk country, has experienced various outbreaks in the 1990s and borders Uganda and the south of Ethiopia where outbreaks have been reported. However, the risk assessment conducted in 2014 did not find evidence of virus circulation, and the antibody seroprevalence in particular was very low. For this reason, Kenya is not included in the list of planned PMVC countries, consistent with the north-eastern part of Ethiopia.

Figure 5. Recommended immunization activities to be completed by country, EYE strategy, 2017–2026



The total target population for Africa is approximately 440 million, requiring 490 million doses of vaccine over 10 years (Table 8).

Sequencing of vaccination activities

Following the prioritization exercise, PMVCs were sequenced based on available vaccines by year. For this we used global vaccine production forecasts for 2017–2026 (see Part 5), deducted estimated needs of countries in LAC and for routine immunization in Africa, and assigned the remaining vaccines to PMVCs in priority order.

According to the proposed schedule, all recommended PMVCs can be completed with the available vaccines within the 10-year time frame of the strategy (Table 8).

Table 8. Proposed sequencing of preventive mass vaccination campaigns over time, Africa

In number of doses (1000s)

Country	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	total
Nigeria	30 694	31 480	32 280	33 093	33 920	0	0	0	0	0	161 467
Ghana	3 057	9 370	3 190	0	0	0	0	0	0	0	15 616
Sudan	0	9 215	14 159	0	0	0	0	0	0	0	23 374
Uganda	0	0	0	14 674	30 285	0	0	0	0	0	44 959
DRC	8 773	0	0	0	0	30 638	31 558	21 664	0	0	92 633
Angola	0	0	0	0	0	9 947	0	0	0	0	9 947
Guinea-Bissau	0	0	0	0	0	0	2 354	0	0	0	2 354
Ethiopia	0	0	0	0	0	31 242	31 940	0	0	0	63 182
South Sudan	0	0	0	0	0	0	8 112	8 310	0	0	16 422
Congo	0	0	0	0	0	0	0	6 221	0	0	6 221
Equatorial Guinea	0	0	0	0	0	0	0	1 147	0	0	1 147
Chad	0	0	0	0	0	0	0	19 762	0	0	19 762
Niger	0	0	0	0	0	0	0	30 402	0	0	30 402
Gabon	0	0	0	0	0	0	0	664	0	0	664
Sum (Africa)	42 523	50 065	49 629	47 767	64 206	71 828	73 965	88 171	0	0	488 153

Notes:

- Population figures taken from UNPD projections for anticipated year(s) of campaign implementation.
- Initial target population = 96% of total, corresponding to >1-year-old population.
- In Nigeria, initial target population is 80% of total, corresponding to 1–45 year-old population. In Ghana, target population is 67% of total, corresponding to those aged 10 years and above.
- For Nigeria, Sudan, DRC, Angola and Ghana, the remaining target population takes into account previous PMVCs.
- The assumed vaccine wastage rate is 10%.
- For DRC, the 2017 number of doses is estimated to be provided as a booster dose to the fractioned dose used in Kinshasa. The need for this strategy will be confirmed with immunological studies.

Catch-up campaigns

Reported immunization coverage will be monitored and the overall vaccine-induced population immunity (PI) (taking into account routine EPI, reactive and preventive campaigns), will be calculated each year, indicating which countries should be targeted for catch-up. The recommended PI

threshold for protection is 70% (being the midpoint of the consensus threshold range for YF herd immunity of 60–80%).

In **Africa**, based on current assessments at the time of drafting the strategy (September 2016), a catch-up campaign is recommended for Gabon only. Gabon was also identified in the middle range PI category (Table 6). It is estimated that 677 000 doses of vaccine will be required, covering in particular the unprotected population currently aged between 10 and 20 years, in order to vaccinate the susceptible population not reached during the national mass vaccination campaign in 1995 and routine EPI since the introduction of YF vaccine in 2003.

In **LAC**, mass preventive vaccination campaigns have been conducted in 10 countries: the Plurinational State of Bolivia (2007), Brazil, and earlier in Colombia, Ecuador, Guyana, Panama, Paraguay, Peru, Trinidad and Tobago and the Bolivarian Republic of Venezuela. Most of these campaigns have targeted populations living in enzootic areas and areas from where migrants originate to enzootic areas. The Plurinational State of Bolivia is the only country to have conducted a national campaign targeting the population aged between 2 and 44 years. Suriname and Panama have not conducted a national campaign, in addition to Argentina where virus circulation is very limited geographically.

Brazil has implemented a unique vaccination schedule, including periodic re-vaccination in endemic areas. This special case falls outside the regional strategy. The total vaccine demand for Brazil, including such campaigns, has been estimated at 30 million doses per year. The particular situation of French Guyana, as a special territory, is not included in the strategy.

It is proposed that catch-up campaigns will be conducted in the 11 remaining countries with enzootic circulation of YF virus (Table 9). Initial vaccine demand is estimated at approximately **39 million doses** (Brazil and French Guyana not included) (Table 10).

Table 9. Needs estimates for preventive mass vaccination against YF targeting high-risk groups in Latin America

Country	Type of campaign	Target population (% country total)	Target population
Argentina	Subnational	1%	433 020
Bolivia (Plurinational State of)	Catch-up	20%	2 217 273
Colombia	Catch-up	20%	9 535 186
Ecuador	Catch-up	5%	832 243
Guyana	Catch-up	5%	37 766
Panama	Subnational	5%	203 085
Paraguay	Catch-up	40%	2 745 865
Peru	Catch-up	20%	6 175 963
Suriname	Subnational	5%	27 308
Trinidad and Tobago	Catch-up	5%	66 211
Venezuela (Bolivarian Republic of)	Catch-up	40%	12 603 443
TOTAL			34 877 363

Table 10. Proposed sequencing of preventive mass vaccination campaigns over time, LAC countries**In number of doses (1000s)**

Country	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	total
Peru	5 147	1 736	0	0	0	0	0	0	0	0	6 883
Colombia	0	2 638	5 318	2 679	0	0	0	0	0	0	10 635
Venezuela (Bolivarian Republic of)	0	0	3 491	3 532	3 573	3 614	0	0	0	0	14 210
Argentina	0	0	0	0	490	0	0	0	0	0	490
Bolivia (Plurinational State of)	0	0	0	0	2 499	0	0	0	0	0	2 499
Brazil	0	0	0	0	0	0	0	0	0	0	0
Ecuador	0	0	912	0	0	0	0	0	0	0	912
French Guiana	0	0	0	0	0	0	0	0	0	0	0
Guyana	0	0	42	0	0	0	0	0	0	0	42
Panama	0	0	222	0	0	0	0	0	0	0	222
Paraguay	0	0	0	0	1 525	1 543	0	0	0	0	3 069
Suriname	0	0	0	0	30	0	0	0	0	0	30
Trinidad and Tobago	0	0	0	0	74	0	0	0	0	0	74
Sum (LAC excl. Brazil)	5 147	4 375	9 985	6 211	8 192	5 157	0	0	0	0	39 066

In-country prioritization:

In countries with large target populations, national PMVCs will be mounted in multiple phases of subnational increments over several years, in a similar way to the introduction of the meningococcal meningitis A vaccine. In those circumstances, in-country prioritization will be required. Campaign phasing will be developed with the countries themselves, on a country-by-country basis, based on the following principles:

- *ecological criteria*: areas of moist savannah, which are the zones of YF emergence, should be given priority;
- *PI*: areas with low PI should be prioritized;
- *pragmatic considerations*, such as:
 - o vaccination activities are not feasible in sylvatic areas during the rainy season;
 - o the YF vaccine being live attenuated, preventive mass campaigns should be conducted at least one week apart from other live attenuated vaccine campaigns, such as the oral polio vaccine or the measles vaccine, to avoid vaccine immunogenicity reduction;
 - o capital cities located near the YF emergence zone (moist savannah) have an increased risk of urban outbreaks and should be prioritized.

In-country prioritization will not be necessary in countries where PMVCs will be conducted within a year (even if conducted in successive phases).

Action 2: Vaccinate every child**Including YF vaccination in routine immunization schedules**

The best way to maintain high levels of immunity in high-risk countries is to ensure that all new cohorts are immunized in infancy. High coverage in successive cohorts of children will gradually ensure that the PI does not decrease after mass vaccination campaigns.

In Africa, all 27 countries at high risk need to protect all infants against YF by introducing the vaccine into the national routine vaccination schedule and ensure that high coverage is achieved. Most

countries at high risk have introduced the vaccine into the national routine immunization schedule already. However, as of September 2016, five out of the 27 countries had not yet done so (Ethiopia, Kenya, South Sudan, Sudan and Uganda). It is expected that these countries will have introduced the YF vaccine into their routine immunization schedules by 2020.

Approximately **20 to 30 million children** (counts increasing from 2017 to 2026 due to natural population growth) will need to be immunized **annually**, representing an annual demand of 35 to 50 million doses. The total vaccine demand for the next 10 years has been estimated at 465 million doses (Table 11). In this forecast, a 40% vaccine wastage rate has been assumed. The proposed year of introduction for the five countries will need to be confirmed. It is assumed that for year 1 of introduction, the demand is 50% of the infant cohort.

Table 11. Annual needs estimates (vaccine doses in 1000s) for routine immunization against YF in the 27 high-risk countries, Africa

Country	VaccDs17	VaccDs18	VaccDs19	VaccDs20	VaccDs21	VaccDs22	VaccDs23	VaccDs24	VaccDs25	VaccDs26
Nigeria	11,371	11,538	11,710	11,887	12,070	12,258	12,449	12,643	12,840	13,040
Ghana	1,415	1,420	1,424	1,430	1,436	1,443	1,450	1,458	1,466	1,476
Sudan	1,069	2,164	2,191	2,220	2,248	2,278	2,307	2,335	2,363	2,391
Democratic Republic of the Congo	5,213	5,325	5,436	5,547	5,659	5,771	5,883	5,995	6,107	6,220
Angola	1,788	1,829	1,871	1,913	1,956	1,999	2,042	2,086	2,130	2,174
Uganda	1,367	2,794	2,855	2,915	2,975	3,036	3,097	3,158	3,219	3,279
Guinea-Bissau	105	106	107	108	109	110	111	112	113	114
Ethiopia	0	2,599	5,243	5,285	5,323	5,358	5,389	5,417	5,441	5,460
South Sudan	0	0	375	763	774	785	795	804	814	822
Congo	272	276	280	284	289	294	300	305	311	317
Equatorial Guinea	47	48	49	49	50	51	51	52	52	53
Chad	1,000	1,023	1,046	1,068	1,090	1,112	1,133	1,155	1,176	1,196
Niger	1,667	1,729	1,792	1,856	1,922	1,988	2,056	2,125	2,195	2,266
Senegal	935	947	960	973	987	1,001	1,016	1,031	1,047	1,064
Cameroon	1,346	1,362	1,378	1,394	1,410	1,426	1,443	1,459	1,475	1,491
Sierra Leone	355	357	360	362	364	366	367	369	371	372
Central African Republic	254	256	258	260	262	263	264	265	266	267
Guinea	747	758	769	779	790	801	812	823	833	844
Côte d'Ivoire	1,353	1,378	1,402	1,425	1,448	1,470	1,492	1,514	1,535	1,556
Liberia	253	257	261	265	269	273	277	281	285	289
Gambia	138	141	144	146	149	152	155	158	161	164
Togo	419	424	430	435	441	446	452	458	464	471
Burkina Faso	1,163	1,185	1,207	1,228	1,251	1,273	1,296	1,319	1,342	1,365
Mali	1,210	1,235	1,260	1,286	1,313	1,341	1,369	1,399	1,428	1,458
Benin	623	633	642	651	660	669	678	686	694	703
Gabon	83	83	84	84	85	85	86	87	87	88
Kenya	0	0	1,296	2,619	2,647	2,677	2,708	2,740	2,773	2,808
Sum (Africa)	34,194	39,867	44,827	47,234	47,977	48,726	49,478	50,232	50,988	51,746

In LAC, all countries have already introduced the vaccine into the routine schedule. The annual vaccine demand for the 13 countries with enzootic circulation of YF virus is approximately **12 million doses**. The total vaccine demand for the next 10 years has been estimated at 119 million doses (Table 12).

Table 12. Annual vaccine needs estimates (Vaccine doses in 1000) for routine immunization against YF in LAC countries

Country	VaccDs17	VaccDs18	VaccDs19	VaccDs20	VaccDs21	VaccDs22	VaccDs23	VaccDs24	VaccDs25	VaccDs26
Peru	998	992	986	981	975	969	962	956	950	944
Peru (travellers)	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250
Colombia	1 202	1 190	1 179	1 167	1 155	1 143	1 131	1 120	1 110	1 099
Colombia (travellers)	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250
Venezuela (Bolivarian Republic of)	982	979	976	973	969	965	961	957	953	948
Venezuela (Bolivarian Republic of) (travellers)	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250
Argentina	185	185	185	184	184	184	183	183	183	182
Argentina (travellers)	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250
Bolivia (Plurinational State of)	410	411	413	414	415	416	416	417	417	417
Brazil	2 921	2 900	2 879	2 857	2 835	2 813	2 790	2 767	2 743	2 719
Ecuador	541	540	539	539	538	536	535	534	532	531
French Guiana	11	11	11	12	12	12	12	12	12	13
Guyana	25	25	25	26	26	26	26	25	25	25
Panama	37	37	37	37	37	37	37	37	37	37
Paraguay	229	230	230	230	230	229	228	227	226	225
Suriname	16	16	16	16	16	15	15	15	15	15
Trinidad and Tobago	30	29	28	28	27	26	26	25	25	25
Sum (LAC excl. Brazil)	9 665	9 646	9 626	9 605	9 582	9 558	9 534	9 509	9 485	9 460

For Argentina, Colombia, Peru and the Bolivarian Republic of Venezuela, workers and travellers (eco-tourists in particular) to endemic zones are a special consideration.

For Argentina, Brazil and Panama, according to the national schedule, the proportion of the targeted child or infant cohort is 15%, 50% and 30%, respectively, corresponding to the proportion of endemic areas.

To avoid re-vaccination practices, a reliable information system (electronic registry) would be needed, including the adult population.

Improving routine immunization performance

Introducing the vaccine into routine immunization programmes is not enough. In many countries routine immunization coverage is low. Exploration of, and an effective response to, reasons for this poor coverage – which are likely to vary between localities – will be key to successfully implementing this element of the EYE strategy.

Some potential approaches include ensuring that the YF vaccine stock is reliable and that health facilities are well supplied, increasing political will to ensure that children are vaccinated, improving the knowledge and awareness of health care workers about the importance of childhood YF vaccination, linking prevention of measles and YF, and clearly defining targets and indicators. Demand creation has to be particularly strengthened, in liaison with stronger community engagement at all levels, communication and social mobilization efforts.

Special attention must be paid to reaching vulnerable and marginalized populations (e.g. street children, displaced populations and refugees).

Action 3: Risk assessments

A comprehensive risk assessment methodology has been designed and applied in a number of countries in the last five years¹. Country results have been successfully used to guide preventive interventions and recommend – or not – preventive campaigns or introduction of YF vaccine into the routine EPI.

In Africa, given the current EYE plan to conduct national preventive campaigns in the remaining 13 high-risk countries, it is currently not recommended to conduct such a risk assessment in those countries systematically.

The risk assessment exercise has value, in case of:

- perception of changing risk in countries at moderate risk;
- assess vaccine needs and prioritization of roll out;
- country or regional request for revised classification, in particular for the IHR.

In addition, countries outside the current at-risk country list might also benefit from such an assessment, for the same reasons. It is recommended that the risk assessment methodology be revised according to these specific objectives.

In LAC, a risk assessment is recommended for Panama, to inform an IHR reclassification. In addition, in the Plurinational State of Bolivia, Guyana and Trinidad and Tobago, a risk assessment would also be useful to provide orientations on the current risk, and take into account recent population dynamics (migration and urbanization) and evolving ecological conditions.

Strategic objective 2: Prevent international spread

The Angolan outbreak showed that a large urban outbreak in a transport hub can rapidly spread to distant countries (11 cases were exported to China). Fortunately, this occurred during a period when temperatures in China were too low for YF vector activity but it demonstrated that there is a serious risk of international spread. Actions needed to prevent this include:

Action 1: Protect high-risk workers

Applies to the 27 countries at high risk for YF outbreaks in Africa and the 13 countries in LAC

Globalization means that workers in a wide range of extractive industries (such as the oil and mining industries) and other sectors (such as construction and forestry) move into and out of YF endemic areas regularly and are at risk of both developing the disease and spreading it internationally. These workers are particularly exposed to sylvatic transmission when the activity is in forests or recently deforested areas.

Within the EYE governance mechanism (see Part 5), a working group involving companies from the major sectors affected (e.g. the extractive, construction and forestry industries, and the transportation sector) and public health experts is needed to develop strategies ensuring that all

¹ http://www.who.int/csr/disease/yellowfev/risk_assessment/en/

international workers are protected. The private sector should be involved in this effort and ensure that staff and their families are protected.

Action 2: Apply the International Health Regulations

Because epidemic risk might exist through imported cases, strict implementation of the IHR for travellers in and out of countries at-risk for YF, as well as increased surveillance and preparedness, will be paramount to prevent, detect and respond to potential epidemic threats. YF vaccination requirements are clearly stated in the IHR, but are not being fully applied. Port and border control authorities need to be engaged to identify gaps and ensure that the vaccination status of all travellers entering and leaving endemic areas is known and appropriately managed. This is particularly important at points of entry in the at-risk countries.

All countries need to engage transportation agencies (e.g. the International Air Transport Association), airlines and border control agencies/customs to strengthen the control of YF immunization status, in line with the IHR, based on area of origin and destination, at entry and departure.

A particular problem is the production of falsified immunization cards or certificates as well as non-official card selling points. In addition to specific country control measures, a solution needs to be proposed at the global level to move towards a unique registration system and the creation of non-falsifiable cards.

Action 3: Build resilient urban centres

Large cities are vulnerable to epidemics: viruses are more likely to be introduced and dense populations enable rapid amplification of transmission. Epidemics in urban settings are particularly disruptive. Building resilience to epidemic risks in large cities is essential for global health security.

Readiness plans

Reducing the risk of epidemics in urban centres can be achieved through increased readiness (e.g. development of urban readiness plans) and the development of risk assessment and intervention plans for transportation hubs.

Urbanization has led to rapid demographic growth in capital cities where the risk of YF urban outbreaks is very high. Some countries have already identified this risk of epidemics and have developed emergency management plans. These are led by specialized agencies (such as the Lagos State Emergency Management Agency¹), with possible focus on high-risk infrastructures such as airports and other transportation hubs,² or health care centres.¹

¹ https://www.facebook.com/permalink.php?story_fbid=488494674631290&id=325518144262278

² "Preparing and responding to a public health event: Montreal Airport", Public Health Agency of Canada, available from <http://www.icao.int/Meetings/CAPSCA2015/Presentations/DAY%201/Session%204/02%20Capsca%202015%20Public%20health%20preparedness%20and%20planning.pdf>

Large urban centres at risk for YF outbreaks or at potential for YF transmission should be prepared to respond to YF outbreaks and develop readiness plans focusing on rapid implementation of an emergency vaccination campaign and control of transmission in transportation hubs (bus and railway stations, airports, ports). These plans should identify key resources and a highly trained core team of health care professionals (public health officers, laboratory experts, patient care and vector control specialists) who will be prepared to manage the entire outbreak response – including rapid risk assessment – and to tap into appropriate networks of experts and resources (e.g. the ICG). Plans will detail coordination between agencies (roles and responsibilities, communication channels) in the preparedness phase (e.g. maintaining an appropriate pool of trained health care workers) as well as during the epidemic (e.g. leadership roles, decision-making, and engagement with partners).

Mass vaccination campaigns have proved to be particularly challenging in urban settings due to the size and logistic challenges of the operation, as well as the mobility of the population. Specific preparedness efforts are needed to ensure timely and rapid vaccination during urban outbreaks.

For Africa: A list of priority cities for readiness plans will be established. A first attempt to identify densely populated cities with low PI and increasing risk of importation or exportation (e.g. with harbours or other transportation hubs) is proposed: Nairobi, Mombasa, Kampala, Khartoum, Lagos, Abuja, Juba, Dar es Salaam, Brazzaville and Libreville.

Sustained vector surveillance and control programmes in cities

Aedes aegypti indices should be calculated regularly in cities at-risk or with potential for YF. This monitoring should be integrated into urban emergency planning and trigger activities based on the estimated level of risk. These measures should be part of broader arbovirus surveillance and readiness in countries at-risk for dengue, Zika, and chikungunya as well.

Vector control requires sustained efforts to maintain low mosquito density, particularly *Aedes* vectors which are well adapted to humans. Qualitative research should be used to understand what does and does not work for *Aedes* control. Strategies involving all parties practically and effectively need to be developed.

Strategic objective 3: Contain outbreaks rapidly

The risk of large urban YF outbreaks has increased due to a combination of factors including rampant informal urbanization. The fast pace at which African cities grow is challenging the capacity of health systems to provide adequate services such as timely epidemic detection and response and prevention of international spread. The recent Angolan outbreak illustrated the heavy demand on international resources and capacity imposed by responding to large YF urban outbreaks.

Outbreaks are unusual events that require additional resources and partners. Planning is essential for a successful response as well as a good coordination of partners.

Rapid containment of an outbreak is essential to prevent amplification into devastating epidemics. It is dependent on:

¹ <https://www.health.ny.gov/environmental/emergency/>

- (i) early detection;
- (ii) emergency vaccine stockpiles; and
- (iii) rapid response.

Action 1: Early detection. Strengthen surveillance and laboratory capacity

As work proceeds to raise population immunity levels, outbreaks will continue to occur. Strengthened surveillance and improved laboratory capacity should be in place to detect outbreaks early and contain them rapidly. In addition, better surveillance and diagnostic capacity provides more information to permit assessment of the evolving risk as well as the impact of preventive and control measures.

In Africa, a network for detection and laboratory confirmation of YF cases in the WHO African Region was established in 2001, with 21 Member States currently participating. This has enabled surveillance objectives, case definitions, investigation and laboratory methods, and other tools to be standardized across the network and to use the same information flow. However, the laboratory capacity in some countries is still too low to ensure early detection of initial cases. **In LAC**, the regional network of laboratories is integrated with arbovirus surveillance (Red de Laboratorios de Dengue de las Américas).

Current challenges include:

- The suspect case definition (fever and jaundice) is sensitive but not very specific; from there very few suspected cases turn out to be true yellow fever cases (less than 2%). This is costly and might discourage the health workers.
- The first level of diagnostic, IgM detected in serum, is not specific enough to confirm a case:
 - o The current test / assay used at national level (IgM detection) is based on in-house ELISA for IgM from US-CDC and Institut Pasteur Dakar, Senegal.
 - o The IgM detection test is generally performed by the national laboratory (usually in the capital city) meaning that samples may need long transportation times thus affecting specimen quality and timely investigation. This causes delays, is cumbersome (cold chain, etc) and is associated with the risks of bad conservation.
 - o For the diagnosis of cases in the *first* phase of disease, the IgM is often negative and therefore detection of YF genome would be the method of choice.
- Because of the lack of national laboratory capacity for confirmation, specimens that give a positive IgM result in any African country has to be shipped to the regional YF reference laboratory for confirmation (neutralization, PCR, etc.), which considerably delays the final diagnostic decision.
- The current laboratory quality control – quality assurance scheme is limited.
- Countries with no laboratories participating in the laboratory network have no recognized laboratory capacity
- Data management is compartmentalized: yellow fever case information is collected in three different databases (epidemiological, laboratory and reference laboratory) but are not linked to each other.

Recommended surveillance strategies

All high-risk countries should be part of the regional surveillance networks. The eight African countries considered at moderate risk should raise their detection and confirmation capacities. A sentinel surveillance approach is the most practical and efficient choice, limiting pressure on resources while achieving adequate capacity.

The countries in the “potential for YF transmission” group are not required to join the regional network but they should, as part of the country control plan, ensure that severe suspected cases (e.g. people with haemorrhagic symptoms) are detected and investigated for YF.

In all countries, the IDSR framework should be the foundation for YF surveillance. Means of optimizing YF detection and confirmation and integrating activities (training, sample transportation, laboratory confirmation, etc.) should be explored and defined in each country. Community-based surveillance through initiatives such as community risk management and early warning social networks should be promoted. YF surveillance and testing capacities need to be integrated with those of other systems, such as for other arboviruses (e.g. Zika and chikungunya), viral haemorrhagic fevers (e.g. Ebola) or other diseases for which stronger capacity was built over time (e.g. HIV).

Strengthening surveillance

To strengthen and extend surveillance, **two axes** will be developed in parallel:

1. Strengthen rapid detection capacity***Adaptation and strengthening of existing case based surveillance***

Priorities include:

- Revision of regional surveillance guidelines including the revision of case definition: testing the usefulness and feasibility of additional symptoms or tests to improve the specificity of the suspected case definition.
- Revision of national YF surveillance guidelines taking into account local needs and differential diagnosis in areas with circulation of other arboviruses;
- Providing specific health worker training to improve differential diagnosis and the collection of vaccination information
- Design and use a regional database management structure to ensure that the epidemiological and laboratory information for each suspected case of YF is linked. Elements needed to achieve this include:
 - o build an Information Technologies (IT) platform permitting the information to be entered and consulted;
 - o the IT platform should allow the visualization of YF cases in space and time, and link the information with immunization activities;
 - o train the various actors involved accordingly.

2. Increase diagnostic capacity

Regional and subregional laboratory confirmation capacity

In Africa, currently there is only one functional reference laboratory in the Institut Pasteur, Dakar. It is necessary to develop additional facilities in the region with genome detection (PCR), and serology (ELISA, PRNT to detect antibodies and neutralising antibodies for YF, respectively) capacity according to international standards. The region will develop a plan to progressively identify and support an increasing number of reference laboratories that will serve neighbouring countries.

Building national laboratory capacity

At the same time, all countries will be supported to increase their own capacity, in particular PCR. A specific issue needs to be addressed concerning sample transportation, particularly cross-border shipping of specimens. Standard Operating Procedures describing the flow of specimen and data must be established and/or enhanced (for the national and, more challenging, international level). It is critical to ensure that those laboratories have sufficient reagents and appropriately trained personnel.

External quality assessment (EQA)/quality control (QC)

Strengthening and expansion of the EQA programme for laboratories performing YF diagnostics (genome detection and serology) should be fully functional for both serology and genome detection. Laboratories need to be accredited and operationalized for standardized laboratory procedures and data management.

New methods to accelerate diagnostic

- Introducing bedside (point-of-care) laboratory techniques to test for other pathogens that cause symptoms and illness similar to YF and meet the same case definition (malaria, leptospirosis, hepatitis A, B, C, D, E).
- development of a robust and rapid diagnostic test for YF genome detection;
- development of new specimen sampling methods (serum, saliva, urine), sample stabilization and transport;
- development of additional serology tests for differentiating between cross-reacting viruses;

Action 2: Ensure emergency stockpile vaccines

Emergency stockpiles ensure timely and equitable access to vaccines during emergencies. It is a critical element to contain outbreaks. In the VIS approved by the Gavi Board, the emergency stockpile estimation was a reducing number of doses over the years from 6 million to a minimum level of 2 million doses in 2022. This estimation was made under the assumption that after mass preventive vaccination campaigns in the 12 highest-risk countries and the decreasing number of YF outbreaks in the period 2011–2015, the need for a large stockpile would decline.

After the large urban outbreak in Luanda and the risk of spread, the ICG members met in July 2016 to review the vaccine needs for the emergency stockpile and discuss a forecast for the next 10 years. Taking in consideration the rapid change in YF the epidemiology in Africa and Latin America, and the current situation in Angola and DRC, the option of increasing the size of the stockpile has been considered. Maintaining a large stockpile was not considered as a the best investment given the low frequency of large outbreaks, therefore the ICG decided to retain the emergency stockpile at the level of 6 million doses. The main difference with the previous stockpiles is in the availability of vaccine: the new stockpile model is to maintain a stock of 6 million doses at any time over a given year – a **Revolving Emergency Stockpile**. The stockpile will be immediately replenished after its use to respond to an outbreak. This strategy will allow the ICG to respond to large urban or long-lasting outbreaks. Vaccine manufacturers should always have a constant level of vaccine in stock ready for shipment. UNICEF Supply Division (SD) will closely work with the vaccine manufacturers to ensure and monitor the fact that 6 million doses of vaccine are always in stock.

The stockpile of 6 million doses will be part of the annual demand for preventive vaccination campaigns; therefore, UNICEF SD and vaccine manufacturers will rotate the stocks between the emergency, the vaccine for preventive campaigns and routine EPI stocks in order to ensure that there is always a minimum of 6 million doses ready for in shipment within 48 hours. With this revolving concept, there will be no wastage due to expiration of vaccine since the vaccine will be used for preventive campaigns.

If a larger outbreak occurs and the demand exceeds 6 million doses, UNICEF and WHO will work together with the vaccine manufactures to reprioritize the vaccine still under production in order to give primacy to the replenishment of the stockpile to return as soon as possible to the level of 6 million doses. To rapidly replenish the stock during long emergencies, of over 3 months, WHO and UNICEF SD will also work with the vaccine manufacturers to optimize/prioritize vaccine supply in 20 dose vials presentation, which could later be used in mass preventive campaigns.

The ICG also decided to continue reviewing the stockpile forecast every year since it is expected that in the context of the EYE strategy the risk of large epidemics will be eliminated, and therefore the need for vaccine for emergency response will be reduced to a minimum stock.

Short- and long-term options to cope with a surge in emergency demand

The 6 million doses in the emergency stockpile should be enough to respond to most urban epidemics in the current endemic countries in Africa and LAC. In case of a larger unexpected outbreak, including in India or China, there is a need for alternatives to enable a rapid increase in production or shorten the production and release lead times.

In the short term, EYE partners will explore with vaccine manufacturers and national regulatory authorities ways of optimizing bulk production capacity, reviewing potency and stability requirements, and increasing the shelf-life of the bulk and the finished product. These will give the manufacturers greater flexibility to stock bulks for long periods, and thus to quickly fill/finish production in case of emergencies and/or vaccine shortages. Extending the shelf-life of the final product will provide manufacturers with more flexibility to rotate the stock and countries with more flexibility in using the vaccine.

In the mid to long term, WHO will also work with vaccine manufacturers to explore and encourage novel vaccine production technologies, such as YF vaccine production based cell-culture or a DNA vaccine (Table 13).

Table 13. Short- and long-term options to cope with a surge in emergency demand

Time frame	Strategy	Advantage
Short term	Expand the shelf-life time of the 5, 10 doses of YF vaccine from 3 years to 5 years	This will give greater flexibility in using stockpiles and will reduce the outdating of still usable YF vaccine
	Expand the shelf-life time of YF bulk material	This will give manufacturers greater flexibility to rapidly fill/finish vaccine in case of unexpected emergencies or long outbreaks
	Long-term storage (1–2 years) of unlabelled or naked vaccine vials at -20°C for immediate approval in case of shortage	This will give manufacturers greater flexibility in preparing vaccine in case of emergencies and vaccine shortage
	Prioritizing 20-dose vials, which might be more suited to mass vaccination campaigns than 5–10-dose vials	This will facilitate rapid replenishment of the stockpile by enabling easy duplication of production capacity
Medium term	Define an upper limit of potency per YF vaccine dose	This will improve the homogeneity of vaccine between the different manufacturers
Long term	Review and revise the YF manufacturing process regarding thermal stability testing (14 days, 37°C ► 7 days, 37°C)	This will allow optimization of vaccine preparation
	Revise the testing of the YF working seed in monkeys by replacement with a molecular analysis.	This will replace animal trials and reduce lead time of QC and costs

Action 3: Rapid outbreak response

An effective yellow fever outbreak response revolves around rapid detection of cases, reactive vaccination, good case management, vector control and community mobilization.

Strengthened outbreak response capacity can be achieved through:

- streamlined YF investigation with an emphasis on assessing the risk of spread in relation to transportation hubs and population movements, PI and vector density. Streamlined YF investigations should include the following:
 - documentation of the geographical extent of the outbreak (transportation hubs, population movements, markets);
 - identification of where and how the epidemic is spreading;
 - systematic, rapid entomological investigations (vector density):
 - it is critical to understand the possible spread of the YF virus (as *Aedes* spp. only travel 100–1000m).

2. rapid laboratory confirmation and adaptation of the case definitions if needed;
3. control interventions
 - efficient reactive vaccination campaigns (achieving high coverage and quality);
 - good case management and increased access to health care centres in order to reduce mortality and improve diagnosis;
 - vector control:
 - elimination of all potential breeding sites or control
 - cleaning campaigns (tyres, empty cans, etc.)
 - covering of reservoirs
 - larvicide
 - spraying to kill adult mosquitoes during an epidemic
 - fogging is most effective when conducted in the hours around dawn and dusk, when mosquito activity is most intense.
 - capture” of the eggs of survivors
 - Ovitrap
4. Partnership and coordination
 - Involvement of multidisciplinary teams to conduct investigation and response interventions (e.g., with the support of the regional GOARN network, development partners, other UN agencies).

Fractional doses

In emergencies, when vaccine supplies are limited, use of a “fractional dose” – one fifth of the normal dose – may be considered. In October 2016, the evidence-base for the use of this strategy will be submitted to the Strategic Advisory Group of Experts (SAGE) for validation. In addition, the evaluation of its use during the current DRC outbreak will guide further practice, and follow-up studies (such as immunogenicity studies) will also provide further evidence.

Part 5: Keys to success

1. Availability of accessible, affordable vaccines and a sustained vaccine market

Since the inception of the YF investment case supported by Gavi, YF vaccine supply has improved significantly. In 2001, only two manufacturers were producing WHO-prequalified YF vaccine. This has now increased to four manufacturers: Sanofi Pasteur (France), Institut Pasteur de Dakar (Senegal), Bio-Manguinhos (Brazil), and Chumakov Institute (Russian Federation). Vaccine production capacity has quadrupled from 20 million to 80 million doses annually.

However, vaccine supply has remained one of the major obstacles to implementing mass vaccination campaigns, especially in countries with large targeted populations. Vaccine supplies available for preventive campaigns have been limited to 15 million people per year, and therefore some countries have had to phase their campaigns over two or three years, slowing down the risk reduction strategy.

Vaccine supply has been continually challenged, mainly by: (i) a sharp increase in demand after the YF investment case; (ii) regulatory and prequalification suspensions; and (iii) production problems, leading to a situation in which supply has been below demand.

Global demand for YF vaccines has increased from approximately 20 million doses in 2001 to 90 million doses on average from 2012 onwards. This growth is mainly due to the demand generated by the resurgence of YF epidemics in Africa and the support provided by Gavi to endemic countries to access the vaccine.

The change in risk shows that the need for YF vaccine has increased. However, the EYE will be successful only if demand and supply are aligned to allow a timely and effective risk reduction strategy. This will require the sustained engagement of the various stakeholders as well as robust mechanisms for need forecasting and market shaping.

Production capacity

The market for YF vaccine is not very attractive for manufacturers: it is small compared with that for other vaccines and the profit margin is low, providing little incentive for manufacturers to produce it. The vaccine is only used in endemic countries and only one dose is needed. The demand for YF vaccine is also unpredictable and very much driven by outbreaks, another disincentive for vaccine manufacturers.

It is not expected that any new manufacturers will begin production in 2017, although production by existing suppliers is expected to increase.

In 2017, global production capacity is expected to rise to between 105 and 132 million doses. There is considerable uncertainty around these figures. However, a rise in capacity is linked to one of the manufacturers being able to increase production through contracting out filling/freeze-drying capacity. There are also uncertainties around yields.

Reliable production

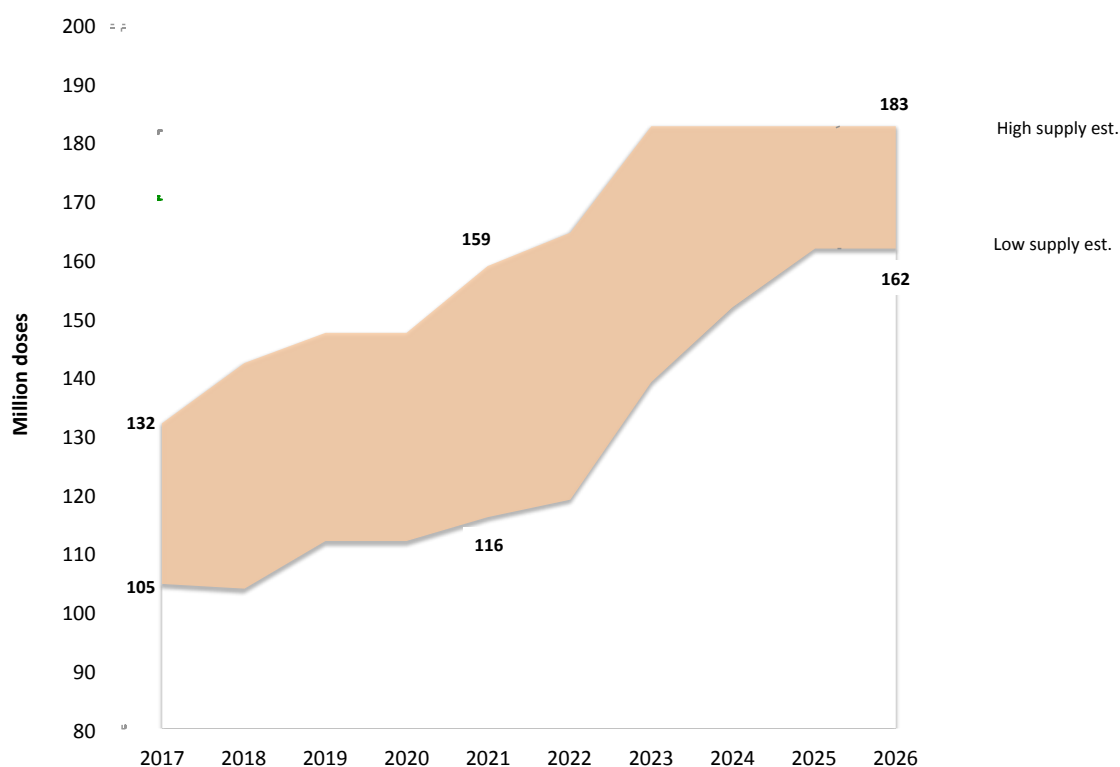
Over the past five years, actual supply has been significantly lower than theoretical production capacity. This was due to quality issues for some manufacturers and/or upgrading work on the production units. As a result, supply was 10–20% below demand. In 2017, reliability is expected to improve because all manufacturers have made investments in production equipment and facilities between 2012 and 2016. However, the YF vaccine production process remains the same and will continue to be technically challenging and prone to unexpected quality or yield issues. It will also remain relatively inflexible to increased demand.

Global supply outlook 2017–2026

The global supply of YF vaccines is expected to increase to between 105 and 132 million doses in 2017, to between 116 and 159 million doses in 2021, and to between 162 and 183 million doses in 2026 (Figure 6).

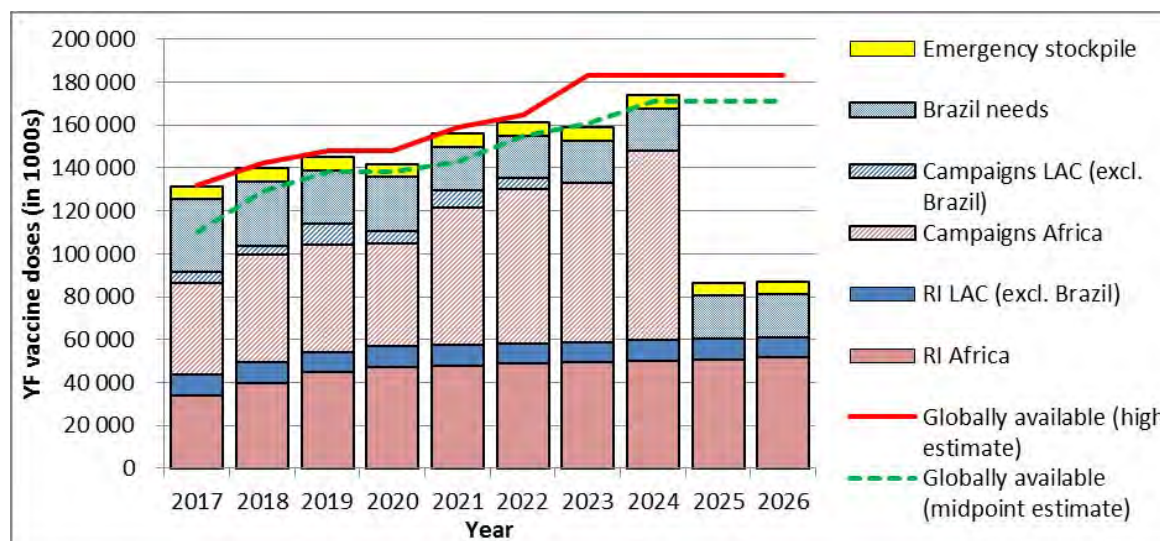
The increased capacity expected during 2017–2020 should be achieved by prioritizing and optimizing YF vaccine production and contracting manufacturer operations for filling and freeze-drying. New production capacity is mainly expected after 2021, when new facilities in two manufacturers will start production.

Figure 6. Estimated global yellow fever vaccine supply (high to low risk-adjusted estimates), 2017–2026 (Source: Gavi. Supply and procurement roadmap Yellow fever vaccine, update August 2016)



When comparing the planned production with current estimates for global demand as presented in this document, the demand fits into the high estimates of the projections (Figure 7). However, the current picture does not include catch-up campaigns for Africa and does not take into account changing risk, as well as production issues, a problem that, as noted above, has occurred regularly in the last five years.

Figure 7. Global YF vaccine demand, by type, 2017–2026



2. Political commitment and sustainable national and regional YF control strategies

In countries at greatest risk of YF epidemics, it is essential that the leadership is committed to preventing epidemics and embraces the need to establish new synergies by providing local expertise and resources to implement EYE. Campaigns and strategies can only work if country ownership is genuine. Where public health strategies, including vaccination, are successful, it is primarily because local people have worked hard to improve the health of their communities and are committed to improving the nation's health. EYE will only achieve its goal of eliminating epidemics if it is the people in affected countries who "lead the charge" against YF epidemics. EYE is a global strategy with regional and country representation.

To achieve political commitment and country buy-in, the EYE strategy must include raising awareness at all levels, from the community to national and international leaders and partners. Understanding of the potentially devastating nature of YF epidemics should increase the eagerness of countries and communities to adhere to the opportunity that EYE offers to prevent this once and for all.

At regional level, the political (regional committee) and technical (TAG) bodies will be requested to endorse the strategies and way forward.

3. Governance and partnerships

The development and the implementation of a YF long-term strategy require the coordination of a number of partners and countries as well as a transparent and effective mechanism for decision-making on strategic tactical and operational issues. This mechanism should be flexible enough to adapt to the evolution of the risk, whether it increases due to external factors such as urbanization, or decreases due to factors such as successful implementation of control interventions.

Based on the existing mechanism in place, such as the YF partnership and the lessons learnt from the past in YF and other disease programmes, EYE:

- Will be led by a **steering committee** composed of a core group and members. The core group of three multilateral stakeholders – UNICEF, WHO and Gavi – guides the overall effort and ensures that members who play a critical role in the effort are engaged and represented. The members are institutions, partner agencies or countries that play a significant role in the implementation of the strategy. The initial list of members will be based on the existing members of the YF partnership (<http://www.who.int/csr/disease/yellowfev/yfvaccine/en/>), but will be open to new members as well. The steering committee will be broad enough to provide expertise relevant to the many areas involved and flexible enough to integrate new partners as needed (e.g. the African Union and private sector partners from the extractive, construction and forestry industries, and the transportation sector).
- The EYE **secretariat** based at WHO will support the steering committee and will propose terms of reference and governance principles for the steering committee (appointment of the chair, criteria for membership, frequency of meetings, relationship between steering committee and working groups and so on).
- In addition to the steering committee, **working groups** will be established as resource groups to address issues within a particular area and to mobilize external expertise for answering specific questions. The working groups will be defined by the steering committee at the inception phase of the strategy. Members of the steering committee are also expected to contribute to the working groups. The working groups will report to the steering committee on a regular basis. There will two types of working groups:
 - (i) **technical working groups** addressing technical and tactical issues in specific areas (e.g. laboratory and surveillance, vaccine market shaping, vector control and so on); and
 - (ii) **regional/subregional working groups** addressing operational issues in implementation of the strategy. Regional immunization TAGs and countries that are to be targeted for the next round of vaccinations should also be included in working groups.

The steering committee will:

- support the design and implementation of the global strategy;
- provide a forum for technical exchange, coordination, and cooperation on YF-related activities;
- coordinate the implementation of EYE strategic approaches and activities;
- continuously monitor and evaluate implementation;
- disseminate information about YF prevention and control;
- encourage continuous engagement of partners, donors and countries;
- support the development of a research agenda taking into account the public health needs.

The secretariat will:

- run stakeholder analyses and maintain a stakeholders list;
- organize meetings of the EYE steering committee;
- organize regular working groups on a planned and emergency basis;
- monitor and evaluate EYE implementation;
- engage with appropriate networks of experts, agencies and sectors, including the private sector and transportation and border control/customs agencies.;
- review EYE progress towards targets and assess public health impact;
- advocate at high level;

4. Acceleration of research and development for new tools and better practices

A broad global coalition of experts with stakeholders, including public health agencies (particularly those in affected countries), academia, the biotech sector, industry, regulators, funding agencies and ethics committees will be formed as a specific working group under the umbrella of the governance body. The group will identify public health research priorities and activities, and ensure that the identified priorities and activities are considered within the WHO R&D Blueprint for Action to Prevent Epidemics.

Specific steps:

- assess the current public health measures for YF prevention and control, and identify the current challenges and knowledge gaps;
- review gaps in key activities at all levels (global, regional and country), minimize unhelpful overlaps, and stimulate priority activities to maintain momentum;
- organize expert consultations to prioritize R&D options to guide control of and response to YF outbreaks.

Current priority research areas include vaccine, vector control, diagnostic and case management issues.

Part 6: Monitoring and evaluation

The EYE governance body will be in charge of monitoring the implementation, performance and impact of EYE activities. The secretariat will liaise with the Decade of Vaccine/GVAP working groups.

Key milestones

By the end of 2017:

- EYE governance body is fully operational
- The implementation plan including indicators and deliverable is ready
- At risk countries are engaged in the EYE implementation

By the end of 2018:

- Three African subregional reference laboratories are fully functional with confirmation

By the end of 2019:

- All African high-risk countries have introduced the YF vaccine into routine immunization;

By the end of 2020:

- Six African subregional reference laboratories are fully functional and an EQA/QC is fully functional for both serology and molecular diagnostic procedures.

By the end of 2021:

- All LAC countries have completed mass immunization campaigns.
- Campaigns have been completed for Nigeria, Ghana and Sudan.

By the end of 2022:

- Seven of the 13 of high-risk countries of Africa have completed national preventive mass vaccination campaigns.

By the end of 2025:

- All African high-risk countries have diagnostic capacity to confirm YF.

By the end of 2026:

- All high-risk countries have completed national preventive mass vaccination campaigns.

Key indicators

The following indicators will be measured on a regular basis:

Implementation and performance

o Preventive mass campaigns:

- number of preventive mass campaigns conducted;
- number of persons vaccinated;
- district-level coverage;
- vaccine wastage rate.

o Routine immunization:

- number of persons vaccinated;
- proportion of districts with coverage level >80%;
- difference between YF and measles coverage (WUENIC);
- number of vaccine stock-outs.

o Laboratory capacity:

- average time for a suspected case to be confirmed (date of confirmation – date of sample taken).

o Vaccine supply:

- ratio annual YF vaccine production/annual projected capacity

o Readiness:

- number of cities that have an Urban Readiness Plans in place, including response to the YF risk.

o Outbreak response:

- number of days in each year during which the emergency stockpile level is at level zero.

Impact

- number of outbreaks, size and spread;
- number of urban outbreaks;
- number of internationally imported cases.

Regular updates

Assessing risk and setting priorities

Risk and priorities for implementation of the strategy will be reviewed annually: it is expected that risk of YF epidemics will evolve throughout the 10-year implementation of EYE as a result of a combination of factors reducing risk, such as increased PI, and factors increasing risk, such as major population movements, state collapse, or climate change. As risk changes, immunization activity priorities will need to be adjusted accordingly.

Learning as we go

Experience gained from EYE's development, implementation, monitoring and evaluation at all levels should be recorded, analysed, and made available on a regular basis, to **build knowledge** and serve as a source of inspiration and resources for other programmes and initiatives.

Fractional dose yellow fever vaccine as a dose-sparing option for outbreak response

WHO Secretariat information paper

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Table of content

1. Preamble	4
2. Introduction	4
3. Background	4
4. International Health Regulations.....	5
5. Vector control measures.....	6
6. Yellow fever vaccine characteristics	7
7. Fractional Yellow fever vaccine immunogenicity when administration through subcutaneous, intramuscular or intradermal fractional dose.....	7
8. Yellow fever vaccine safety when administered as a fractional dose	11
9. Considerations related to regulatory approval.....	12
10. Programmatic considerations	13
11. Surveillance and monitoring	17
12. Ethical considerations	19
13. Recommendations	21
14. Research needs	22
15. Annexes.....	23
16. References	39

1. Preamble

This document is a summary of the World Health Organization (WHO) secretariat paper in response to the Yellow fever (YF) outbreak in Africa 2016, which has been discussed with YF experts and has been reviewed by WHO's Strategic Advisory Group of Experts (SAGE) on Immunization. The development of this paper was led by the WHO Initiative for Vaccine Research gathering inputs to specific sections from the Pandemic and Epidemic diseases, Essential Medicines, and Immunization Vaccines and Biologicals departments of WHO. The Secretariat paper benefited from input by SAGE and the proposed recommendations were vetted by SAGE. This document will be further updated as additional data become available. A full review on the use of YF vaccine fractionate dose will be conducted by SAGE in October 2016.

2. Introduction

Ongoing YF outbreaks are sharply increasing the demand for YF vaccine, exhausting the global stockpile and putting at risk the immunization of endemic populations. With the campaigns planned, there is now shortage of vaccine, which could increase further if expansion of outbreaks would require additional immunization campaigns at large scale. Hence, there is a need to assess immediate opportunities to increase availability of vaccine in response to ongoing outbreaks that deplete available supplies. This secretariat paper reviews the existing evidence on dose-sparing strategies through fractional dosing of YF vaccine as an immediate and short-term option in response to eventual large scale campaign needs, and makes recommendations for fractional dose vaccination in case of imminent need. This is not intended to serve as longer-term strategy nor to replace established routine immunization practices. Once an outbreak threatens supply capacities, e.g. spreading into highly populated areas, suggestions from this paper shall be considered to support efforts to introduce fractional vaccine dose use.

3. Background

YF is a mosquito-borne viral disease of humans, which can be asymptomatic or cause a wide spectrum of disease, from mild symptoms to severe illness with bleeding, jaundice and, ultimately, deathⁱ. Wild-type YF virus induces lifelong protection against subsequent infection. YF is endemic in countries in the tropical regions of Africa and South America. The vast majority of reported cases and deaths (>90%) occur in sub-Saharan Africa, where YF is a major public health problem occurring in epidemic patterns. Based on data from 2013 from African countries, analysis suggest a burden of 84 000 – 170 000 severe cases and 29 000 – 60 000 deaths due to YF. Due to the existence of an enzootic sylvatic transmission cycle among non-human primates, the disease cannot be eradicated. However, prevention through vaccination can limit the morbidity and mortality of the disease. There are two immunization strategies: 1) delivery of YF vaccine in endemic settings via routine childhood immunization programs, and 2) mass

ⁱ Vaccines and vaccination against yellow fever WHO Position Paper – June 2013. WER. No. 27, 2013, 88, 269–284. <http://www.who.int/wer/2013/wer8827.pdf?ua=1>, accessed June 2016

vaccination campaigns to catch-up on immunization in unvaccinated cohorts not eligible for routine immunization or in response to an outbreak of the disease.

Although YF vaccination is very effective, where implementation of immunization recommendation was suboptimal or even non-existent in some countries, the disease has recurred, leading to major outbreaks in countries where the disease was considered to be under control or disappeared.

By definition, YF outbreaks may constitute one or more cases. Currently, YF outbreaks are ongoing in Africa (Angola, Democratic Republic of Congo (DRC) and Uganda) as well as in South America (Brazil, Colombia, and Peru). As of 7 June, 2945 suspected cases and 329 deaths have been reported from Angola. Of these, 819 cases and 108 deaths were laboratory confirmed. In DRC, 57 cases were confirmed as of 7 June, of which 51 are imported from Angola, 6 are autochthonous (2 Kinshasa, 1 Kwango, 1 Congo Central; and 2 from the Northern provinces (not related to this outbreak)). In Uganda, as of 7 June, a total of 68 suspected cases including 7 confirmed cases were reported. The most recent situation report is available on the WHO website.ⁱⁱ Imported cases among unvaccinated individuals have been reported from China (n=11), Morocco (1 suspected case) and Kenya (n=2 cases).

4. International Health Regulations

YF is the only disease specified in the International Health Regulations (IHR (2005)) for which countries may require proof of vaccination from travellers as a condition of entry under certain circumstances and may take certain measures if an arriving passenger is not in possession of such a certificate. WHO publishes a list of countries with risk of YF transmission and countries requiring YF vaccination, which has been updated in February 2016ⁱⁱⁱ. However, in practice, the vaccination requirements are unevenly applied, and for example many international workers in Angola were not vaccinated at the start of the outbreaks. To interrupt the international spread, it is urgent and essential that the IHR (2005) is reinforced by requiring travellers to present YF vaccination certificates. The feasibility of implementing this measure at land crossings remains a challenge, and may not be logistically feasible given the porous borders at land crossings.

Annexes 6 and 7 to the IHR (2005) indicate that YF vaccine used must be approved by WHO. Also, Annex 7 was amended in 2014^{iv} to indicate that a single dose of the vaccine is enough to confer immunity for life, and that validity of vaccination certificates extends to the life of person vaccinated. Starting on 11 July 2016, this amendment enters into force, and all countries must abide by this new requirement^v.

An Emergency Committee (EC) regarding YF was convened by the Director-General under the International Health Regulations (2005) (IHR 2005) on 19 May 2016. The WHO Director-General accepted the Committee's assessment that the current YF situation is serious and of great concern and

ⁱⁱ WHO Yellow Fever situation report. <http://www.who.int/emergencies/yellow-fever/situation-reports/26-may-2016/en/>, accessed June 2016

ⁱⁱⁱ <http://www.who.int/ith/2016-ith-annex1.pdf?ua=1>, accessed June 2016

^{iv} World Health Assembly Resolution WHA 67.13

^v <http://www.who.int/ith/annex7-ihp.pdf?ua=1>, accessed June 2016

requires intensified control measures, and urged Member States to enforce the YF vaccination requirement for travellers to and from Angola and the Democratic Republic of the Congo in accordance with the IHR (2005), as per the Annex 7 of the IHR (2005)^{vi}.

Recognizing the limited international supply of YF vaccines, the Committee advised the immediate application of the policy of 1 lifetime dose of YF vaccine^{iv} and the rapid evaluation of YF vaccine dose-sparing strategies by the WHO SAGE. This briefing note is prepared to inform SAGE in case of an emergency in which SAGE will be asked to provide their feedback on dose-sparing options. A formal evaluation by SAGE is envisaged for October 2016.

Fractional dose administration of YF vaccine, as discussed in this paper, should not be considered equivalent to full dose vaccination, and until further data have been generated it does not constitute a sufficient dose of YF vaccination in the sense of the IHR.

5. Vector control measures

The incidence of YF is increasing, especially due to infection in metropolitan areas with growing human population densities and urban environments that provide mosquitos with various oviposition sites. Increased urbanization in particular among poorer parts of the population without access to proper water supply and to basic health services as well an increase of international travel both have the potential to further contribute to increased densities of *Aedes aegypti*.

There are no specific data available on vector control measures used in the context of implementing YF vaccination. However, well implemented vector control programmes using existing tools and strategies have been found to be effective in reducing the transmission of Aedes-borne diseases (WHO Vector Control Advisory Group 2016), and can therefore contribute to risk reduction. Improving the quality and extent of implementation of vector control interventions can ensure improved impact against Aedes-borne diseases such as YF.

In particular in a low resource context, country commitment, intersectoral collaboration and capacity building for entomological surveillance, as well as sustained effective control and a rapid outbreak response is critical success factors to strengthen vector control measures.

Interventions that bear the potential to reduce the risk of YF virus transmission include targeted residual spraying on Aedes mosquito resting sites; space spraying inside houses where Aedes mosquito rest and bite; larval control through source reduction and larvicide; and personal protection measures using appropriate repellent and clothing. Furthermore, aggressive promotion and implementation of vector control measures and appropriate personal protective measures can reduce the risk of exposure to circulating YF virus.

^{vi} <http://www.who.int/mediacentre/news/statements/2016/ec-yellow-fever/en/>, accessed May 2016

6. Yellow fever vaccine characteristics

YF vaccines are recommended to be given as a single dose (0.5 ml) injected subcutaneously (SC) or intramuscularly (IM). The evidence in this briefing note is mostly derived from SC route of administration. Healthy individuals rarely fail to develop neutralizing antibodies after vaccination. Clinical trials have found that 80%–100% of vaccine recipients develop protective levels of neutralizing antibodies within 10 days and 99% do so within 30 days. Protection appears to last for life. Limited data suggest that seroconversion is somewhat lower in children below 2 years of age, but the clinical relevance of this is uncertain.^{vii} No evidence on potential differences in immunogenicity and efficacy between SC and IM administration could be retrieved.

All the current commercially available YF vaccines are live attenuated viral vaccines from the 17D lineage. According to current WHO recommendations on quality, safety and efficacy of live attenuated YF vaccines^{viii} the immunizing dose recommended for use should not be less than 3.0 log₁₀ i.e. 1000 international units (IU). The release specifications should be approved by the National Regulatory Authorities (NRA).

There are two YF sub-strains in use currently for manufacture of YF vaccine, namely YF 17DD and YF 17D-204. YF 17D-213 is a derivative of 204, but differs significantly as it has gained a glycosylation site in the E protein. 17D-204 is used by Sanofi, and Institut Pasteur Dakar (at different passage levels), 17D-213 is used by Federal State Unitary Enterprise of Chumakov Institute, and 17DD is used by Bio-Manguinhos, Brazil.^{viii} Therefore, extrapolation of clinical trial data between different products, in particular of different sub-strains, should be done with caution.

7. Fractional Yellow fever vaccine immunogenicity when administration through subcutaneous, intramuscular or intradermal fractional dose

Two recent reviews on dose-sparing strategies were considered. (1) A review of the evidence for a dose-sparing strategy for YF vaccine by ID administration was conducted by the Program for Appropriate Technology in Health (PATH) in 2013. In summary, the authors of this report consider that this approach could be implemented in the short to medium term, as long as clinical evidence for non-inferiority, safety, and dose levels has been generated. It could also be useful in public health emergencies when there might be an acute shortage of YF vaccine. (2) A systematic review by WHO of recent evidence on the fractional dose administration through normal route (SC/IM) and ID administration of YF vaccine. Since the review of PATH additional scientific data were generated by Martins et al (2013) and Campi-Azevedo et al (2014). The WHO search strategy is outlined in Annex 1.

^{vii} Gotuzzo E. et al., Efficacy and duration of immunity after yellow fever vaccination: systematic review on the need for a booster every 10 years. *Am J Trop Med Hyg* 2013

^{viii} WHO TRS 978 Annex 5 http://www.who.int/biologicals/expert_committee/TRS_978_61st_report.pdf, accessed May 2016

While Lopes et al dates from 1988, there are two recent vaccine trials studying safety and immunological non-inferiority: Roukens et al (2008) studying the ID administration of YF vaccine, and Martins et al (2013) and Campi-Azevedo et al (2014) studying IM/SC vaccine administration (same cohort, but different analysis). All studies demonstrated seroconversion and geometric mean titers (GMT). Both fractional dose via IM/SC and ID delivery showed similar immunogenicity as full dose.

The following table summarizes their findings.

Table 1: Publications assessing immunogenicity of the use of fractional dose via usual route of delivery or ID delivery.*

Characteristics	Study #1 Lopes O et al. 1988 (5)	Study #2 Roukens AH et al. 2008 (6)	Study #3 Martins RM et al. 2013 (7)	Study #4 Campi-Azevedo AC et al. 2014 (8)
Study site	Rio de Janeiro, Brazil	The Netherlands	Rio de Janeiro, Brazil	Rio de Janeiro, Brazil
Dose-sparing approach and route of delivery	Fractional dose, IM/SC	Fractional dose, ID vaccination	Fractional dose, IM/SC	Fractional dose, IM/SC
YF vaccine	All YF vaccines came from the same seed lot which complied with WHO min requirements for biological substances (1976)	All administered vaccines originated from Stamaril, Lot # Y5597, Sanofi Pasteur, France.	Experimental products by Bio-Manguinhos having 6 different viral particle concentrations in IU/dose.	Bio-Manguinhos, same vaccine recipients and study #3
Subdose	1/5 th of 1000 PFU	1/5 th of full dose (which was 3.5 x 10 ⁶ PFU)	Full dose of 27,476 IU (NIBSC reference) and five lower alternative formulations (31IU, 158IU, 587IU, 3013IU, 10447IU)	Full dose of 27,476 IU (NIBSC reference) and five lower alternative formulations (31IU, 158IU, 587IU, 3013IU, 10447IU)
Sample Size	259 healthy males	175 participants, healthy adults of 18 years and older (up to 70, mean age 25-27)	749 healthy, adult, army males, not previously vaccinated against YF, mean age 19.4y; around 90% of subjects were seropositivity for Dengue virus and 12-23% for YF at baseline (the latter excluded from PP analysis)	749 healthy, adult, army males, not previously vaccinated against YF; mean age 19.4 years
Study design	Volunteers were allocated to each vaccine group in the order in which they reported for inoculation	Randomized controlled trial to test for immunological non-inferiority. Participants received ID vaccination 0.1 ml or SC vaccination 0.5ml. 155 were primary vaccinated participants (primovaccines), 20 revaccines	A double blind, randomized clinical trial to test for immunological non-inferiority.	Randomized control trial. Compared kinetics of biomarkers (serum chemokine and cytokine) triggered by the full dose and the five lower alternative subdoses of currently used doses of 17DD YF vaccine.
Follow up period	28d	1 yr	10 mos	1 yr
Data collection	The amount of PFU and LD ₅₀ requiring seroconversion were assessed by 8 different varying doses of vaccine. Blood samples were obtained before and 28 days after vaccination. No peak time.	Virus neutralization 80% and virus RNA were evaluated to assess the vaccine efficacy. Primovaccines: Blood samples were collected before vaccination, 4 wks and 8 wks after vaccination. Revaccines: Blood samples were collected before vaccination, 5d and 2 wks and 1 yr after vaccination.	PRNT 50%, viral RNA, and GMTs were evaluated to assess the vaccine efficacy. The occurrence of adverse events were evaluated among volunteers who recorded them on their diaries during the first 10 d after vaccination. No peak time.	PRNT, virus RNA, chemokines and cytokines were evaluated to assess the vaccine efficacy as follows: PRNT80%: Day 0, 30, 365 RT-PCR: Day 3, 4, 5, 6, 7 Chemokines & Cytokines: Day 0, 3, 4, 5, 6, 7, 15, 30
Vaccine Efficacy (defined as seroconversion and immune response titres)	The inoculation of 200-500 PFU induced seroconversion in 100% of participants. The amount is much lower than the minimum required standard by WHO of 1,000 PFU.	From 2 wks to 1 yr after vaccination, the max. serum-dilution (1:16) at which 80% of virus plaques were neutralized did not differ between those given a reduced ID or standard SCs dose. In all cases the WHO standard of seroprotection was reached.	Seroconversion: 97% (except fractions lower than 587 IU). The duration of immunity had no statistically significant difference among groups except 31 IU group.	A less than 1/46 th -fold dose of YF vaccine (587 IU) is able to trigger similar immunogenicity, as evidenced by significant titers of anti-YF PRNT. Analysis of serum biomarkers in association to PRNT and viremia, support 10-fold lower subdose (3,013 IU) of 17DD-YF vaccine.
Vaccine Safety	No description	Redness, swelling and itching were reported more by ID group. 3 SC part. rated events as severe.	No serious adverse events were reported from all groups.	No description
Other aspects		No difference in immunogenicity observed between females and males,	Doses below 587 IU (158 and 31IU) were inferior to full dose; viraemia unrelated to vaccine dose	
Limitations		Small sample size, no stratification by age, modified PRNT).	Small non-representative population, and narrow age range	Small non-representative population, and narrow age range

*For risk of bias assessments, see Annex 3. Unit of potency presented as in the publication.

Intradermal administration of a fractional dose

Roukens et al. demonstrated that ID of 17D-204 YF vaccine with 1/5th of 0.5ml (full dose) could induce the same immunogenicity as the SCs delivery of a full dose. (6) Within this randomized control trial, participants received 0.1 ml (1/5th of full dose) ID or 0.5ml SC. From 2 weeks to 1 year after vaccination, the maximal serum-dilution at which 80% of virus plaques were neutralized (e.g. neutralizing antibody titers) did not differ between vaccinees given a reduced ID or standard SC dose. In all cases the WHO standard of seroprotection was reached (See GRADE table 2, Annex 2).

Fractional dose using the normal route of SC administration

Lopes O et al. showed that seroconversion occurred following administration of 17DD YF vaccine in 100% of the participants in 28 days which is 1/5th to 1/2 of the WHO required dose; but the vaccine was based on older vaccine formulations of the product and therefore of limited interest. The recent randomized controlled trial assessing fractional dosing via regular route of administration using 17DD YF vaccine produced by Bio-Manguinhos (Martins et al., 2013; Campi-Azevedo et al., 2014) are of greater interest. Martins showed that even a 46x dilution resulted in equivalent humoral response as the full dose. Seroconversion occurred in 97% of the participants at 30 days at 1/46th of full dose (Martins RM et al), and neutralizing antibody titres achieved equivalent titres to the full dose. Campi-Azevedo et al. did further investigation into viraemia and chemokine and cytokine responses. Viremia pattern was equivalent to full dose down to a dilution of 1/9 (3013 IU), whereas the 1/46 dilution (587 IU) showed a somewhat reduced and delayed viraemia peak. For the 1/46 dilution, slight differences were also seen in relation to pro-inflammatory cytokines, while serum cytokines were equivalent to the full dose (8).

It should be noted that the Martins/Campi-Azevedo study used vaccine of high potency of above 10000 IU (27,476 IU), and hence even the nine-fold dilution contained three times more IU than the lower threshold recommended by WHO. A considerable range of potency in routine vaccine batches has been reported from all manufacturers (WHO informal consultation of the minimum potency specifications for YF vaccines, 2007) ranging from 1995 log₁₀ IU to 2511886 log₁₀ IU/dose (a more than 1000-fold difference). Hence interpretation of non-inferiority results seen with fractional doses need to be normalized by the actual vaccine potency expressed in IU.

In summary, the above findings are encouraging and document the potential of fractional dosing (see GRADE table 1, Annex 2). Based on the data from Martins and Campi-Azevedo, a fraction dose containing about 3000 IU could be considered equivalent to a full dose and should be considered as preferential dose volume for fractional vaccine doses. Below this value (about 3000-600 IU), protective, but possibly less than life-long protection need to be assumed. Dose fractioning below a potency of about 1000 IU/dose is not advisable, to leave a safety margin to 600 IU below which the humoral immune response was inferior to higher potency doses.

The limitations to the evidence available are the following:

- Study populations are likely different from the populations living in YF endemic areas, both in relation to *flavivirus* exposure and genetic background.

- SC immunization data are only available from one manufacturer using YF 17DD vaccine.
- Children and immunocompromised populations (and women for the fractional dosing (IM/SC) are not included in the studies to evaluate immunogenicity and safety in these subpopulations.
- Long-term duration of immunity beyond one year is unknown with a dose-sparing approach.

Actual doses of YF virus particles in each lot of all prequalified companies are different and vary across lots and stage of expiry, which is important to address if considering the use of a fractional dose.

8. Yellow fever vaccine safety when administered as a fractional dose

The most common systemic side effects after full dose YF vaccine include headache, asthenia, myalgia, malaise, fever, rash and chills. Urticaria is uncommon. Allergic reactions are extremely rare, occurring at an incidence of less than 1 per million, with reactions occurring principally in persons with known egg sensitivity^{ix}. In clinical trials, non-serious adverse events were reported by 25% of vaccinees receiving a full dose of YF vaccine. Serious adverse events following immunization (AEFI) with a full dose of YF vaccine are rare (1 by 2 million people vaccinated in preventive campaigns).

Serious adverse events related to vaccination include YF vaccine-associated viscerotropic disease, neurological diseases, and severe hypersensitive reactions. The available data suggest that the incidence of acute viscerotropic disease following YF vaccination ranges from 0 to 0.21 cases per 100 000 vaccine doses in regions where YF is endemic, and from 0.09 to 0.4 cases per 100 000 doses in populations not exposed to the virus. Neurological (or neurotropic) disease is estimated to occur with a frequency of 0.8 cases per 100 000 vaccine doses administered.^{i,x,xi}

The available data on adverse reactions after fractional doses of YF vaccine are limited to the studies described before and the number of persons vaccinated is too low to appropriately assess the rate of rare but serious adverse events (SAE). A recent study^{xii} to compare the immunogenicity and safety for 5 alternative formulations for YF vaccine, with lower concentrations of viral particles reported no SAE attributable to the vaccine. It is, however, difficult to draw conclusions on SAE with this small sample size. Headache and fatigue were the most frequent symptoms, being reported by more than 1/5th of volunteers. Among 749 volunteers in the study, over 15% reported fever $\geq 37.5^{\circ}\text{C}$ and 2% $\geq 39^{\circ}\text{C}$. Pain, arthralgia, pruritus and nausea were also reported. There were no differences in the frequency of common adverse events, with exception of pain, found more frequently with the full dose vaccine.

^{ix} Vaccines, SIXTH EDITION, STANLEY A. PLOTKIN

^x Detection and investigation of serious adverse events following yellow fever vaccination. Guidance from an informal consultation of experts. 18–19 November 2008. Geneva, Switzerland

^{xi} Risk of yellow fever vaccine-associated viscerotropic disease among the elderly: a systematic review. Rafferty et al Vaccine 2013, 31(49):5789-805

^{xii} 17DD yellow fever vaccine A double blind, randomized clinical trial of immunogenicity and safety on a dose-response study Reinaldo M. Martins et al

In another study^{xiii}, in 155 primary vaccinated participants, ID vaccination evoked redness and swelling at the site of inoculation more frequently and for a significantly longer period than after subcutaneous vaccination. Itching at the site of injection was also reported more by ID vaccinated. The subcutaneously primovaccinated participants reported significantly longer pain at the site of injection and also myalgia compared to the fractional dose. The severity of adverse events due to vaccination, which was reported on a 4-level scale (–, +/–, +, ++), did not reveal a difference in experienced discomfort (both local and systemic) between the ID and SC group.

It has been argued that lower doses of live *flavivirus* vaccines might be associated with deleterious safety effects^{xiv}. This is primarily based on the observation that viraemia of the vaccine virus does not correlate with infectious dose^{xv}. A common explanation is that high virus replication compensates for a small inoculum. However, Campi-Azevedo et al. showed that viraemia intensity stays the same throughout all fractional doses steps down to 3,000 IU, and does not increase and is of the same duration at lower doses. Furthermore, a direct correlation of lower doses of YF vaccine with increased reactogenicity or SAE's has not been described and there is absence of data indicating an increase of severe side effects (viscerotropic complications) when using a fractional dose. Active surveillance systems to report and respond to AEFIs is recommended during the introduction of YF vaccines in fractional doses.

9. Considerations related to regulatory approval

The recommendations on fractionate dose administration of YF vaccine discussed in this paper constitute an off-label use of the vaccine. Similarly, vaccine administration via ID route is an off-label use of the vaccine. Exploring other potential strategies on the dose optimization to increase supply or surge capacity is of critical importance. Risk management of the proposed use of a fractional dose should be addressed as well as all implications on a short and long term basis that require clinical, regulatory and programmatic assessments. Regulatory strategies are lengthy and may be promising in the medium- or long-term but cannot be considered as solutions in the short term for off-license and emergency use.

Considering that available data are restricted to specific manufacturers and their specific viruses, and variability of the manufacturing process leading to different vaccine titers, extrapolation to all YF vaccines requires careful consideration. Product specific data are needed to support the regulatory approval and consequent prequalification of the new dose. Dose reduction efforts must be accompanied with relevant stability data and clinical data.

xiii Intradermally Administered Yellow Fever Vaccine at Reduced Dose Induces a Protective Immune Response: A Randomized Controlled Non-Inferiority Trial. Anna H. Roukens et al Plos One. 2008; 3(4): e1993

xiv Innate and adaptive cellular immunity in flavivirus-naïve human recipients of a live-attenuated dengue serotype 3 vaccine produced in Vero cells (VDV3). Sanchez V. et al, Vaccine 2006

xv Chimeric live, attenuated vaccine against Japanese encephalitis (ChimeriVax-JE): phase 2 clinical trials for safety and immunogenicity, effect of vaccine dose and schedule, and memory response to challenge with inactivated Japanese Encephalitis Antigen. Monath TP et al., Journal of Infectious Diseases 2003.

As a medium-term strategy to increased vaccine supply, exploration of the introduction of an upper potency limit should be considered by manufacturers and regulators. This approach is already practiced by one manufacturer. If the manufacturer needs to change the target potency during manufacturing, then they need to demonstrate to the NRA and later PQ, that there is no impact of this change in the quality and efficacy of the vaccine, as well as no impact on shelf-life of the vaccine.

In relation to the rubber seal of multi dose vials and its resistance to multiple punctures, no specific prequalification guidelines are available. At national level, ISO or pharmacopeia standards are being applied. No direct evidence could be retrieved on the durability of the rubber seal when applying more punctures than indicated per multidose vial. Also, measures to appropriately monitor any programmatic issues in practice should be included in campaigns as a precautionary measure. Currently, efforts on fraction dose use with IPV vaccine are ongoing in India. These may provide lessons learnt on practical aspects of fraction dose use with 10 dose vials.

10. Programmatic considerations

Members of the WHO Immunization Practices Advisory Committee (IPAC) provided insight to the following programmatic considerations via an informal consultation.

The four WHO prequalified YF vaccines are currently available in 2, 5, 10, and 20 multidose vials that need to be reconstituted with excipient diluent (water or saline, depending on manufacturer). Before reconstitution, the lyophilized vaccine can be stored at 2-8 °C for a period of up to 2 or 3 years (see Table 2). Due to the limited heat stability of YF vaccine after reconstitution, opened multi-dose vials of YF vaccine must be kept between +2°C and +8°C, and must be discarded at the end of the immunization session, or within six hours of opening, whichever comes first. All WHO prequalified YF vaccines are attached with a vaccine vial monitor type 14 (VVM 14), which means the vaccines can withstand cumulative exposure to 37°C for up to a period 14 days and still retain potency.

Table 2: WHO Prequalified YF vaccines and their characteristics^{xvi}

Manufacturer	Vial Size (doses)	VVM type	Shelf Life (months)	Indicated storage Temperature	Cold chain volume (cm ³ per dose)
Sanofi Pasteur	10	14	36	2-8 C	2.46
Bio-Manguinhos	5	14	24	2-8 C	6.31
	10	14	36	2-8 C	2.96
	50 (currently not available)	14	24	2-8 C	0.63
Chumakov Institute	2 (very limited for travellers)	14	24	2-8 C	7.2
	5	14	24	2-8 C	6.0
	10	14	24	2-8 C	3.6
Institute Pasteur Dakar	5	14	36	2-8 C	2.8
	10	14	36	2-8 C	1.4
	20 (upon request)	14	36	2-8 C	0.7

Administered as a full dose, YF vaccines are injected as a single dose (0.5 ml) either SC or IM. All YF vaccines come with a vaccine vial monitor Type 14 (VVM 14).

According to current practice, administration of YF vaccines through preventive mass vaccination campaigns is recommended for target groups in areas at risk of YF where there is low vaccination coverage. Vaccination should be provided to everyone aged ≥ 9 months, in any area with reported cases. Noting that YF vaccine is a live attenuated viral vaccine, a risk-benefit assessment should be undertaken for all pregnant and lactating women^{xvii}. YF vaccine can be administered simultaneously with other vaccines.

Fractional-dose vaccine administration

For ease of implementation, a dose-sparing approach for YF vaccine should preferentially keep the same mode of delivery as routinely used vaccine in the country using traditional injection equipment. Diluting the vaccine with a larger volume than recommended by the manufacturer while maintaining a 0.5ml dose to achieve dose sparing is not advised due to programmatic and safety concerns. A fractional dose approach should consist of administration of a volume of not less than 0.1 ml using the standard SC or IM route of administration. Administering a smaller volume of vaccine leads to difficulty in administration such as oozing/loss of volume at injection site, difficulty in availability of appropriately graduated auto-disable (AD) syringes, etc.

^{xvi} Adapted from https://extranet.who.int/gavi/PQ_Web/, accessed June 2016

^{xvii} WHO Position Paper June 2013: Vaccines and vaccination against yellow fever (available at <http://www.who.int/wer/2013/wer8827.pdf?ua=1>, accessed June 2016)

If fractional dosing of YF is to be adopted, it is recommended that the dose is administered using the same technique to which vaccinators are accustomed in their daily practice. Most of the injections provided through the immunization programmes are administered IM or SC. For more information on experience in the routine immunization programme with delivering vaccines ID see Annex 5. For Stamaril® (Sanofi), a country may opt to administer the vaccine via ID route, which is off-label, if experienced in the administering via this route. Otherwise, the Sanofi vaccine should also be administered by the SC route.

Wastage

Since opened vials of YF vaccine should be typically discarded no later than 6 hours (50 dose vial requires discarding after only 4 hours) after opening or at the end of the immunization session (whichever comes earlier), fractional dose administration could theoretically increase wastage. Data for YF mass vaccination campaigns, indicate a 5% wastage rate (similar to measles and rubella vaccine campaigns that have similar handling characteristics) for 10 or 20 dose vials. This is significantly smaller than the indicative wastage rates for routine immunization. As 2 and 50 dose vials are not available and 5 dose immunization are reserved for routine immunization, typically 10 dose vials are considered for use in vaccination campaigns.

Based on this, it could be expected that the administration of YF vaccination through wide age range campaign could result in an effective use of the multi-dose vials, even the larger presentations, if the following aspects are considered:

- Different vial presentation in densely populated/urban and rural settings: larger vials to be used in densely populated or urban settings.
- Different vial presentation for different age groups: some of the countries at risk have very young populations; for instance, Angola's population, is one of the youngest in the African continent, with nearly half of the population under 15 years of age. School (primary and secondary) based vaccination could target large number of children and support the use of larger vials.
- Timely reconstitution of the vaccine, based on the availability of the requisite number of patients.
- Training: for this aspect see section below.

Global supply of injections devices

Implementation of fractional dose use of vaccines would entail a multifold increase of injection devices with a smaller volume compared to the full dose. Dose fractioning strategies have to be therefore based on sufficient availability of suitable injection devices..

WHO is exploring availability of vaccines with various manufacturers for potential use in emergency campaigns.

Vaccine management and handling

Currently, the vial presentations of WHO prequalified YF vaccines are 2, 5, 10 and 20 doses. If used in a ½ dose approach, this essentially equates to the equivalent of 4, 10, 20 and 40 dose vials, and for a 1/5th

fractional-dose approach (0.1ml) to the equivalent of 10, 25, 50 and 100 dose vials. Clearly from a practical standpoint, and given their availability and information secured to date on the stopper, 10 dose vials are the best-available choice for mass campaigns (rapid consumption).

Multiple countries' experiences with implementation of wide age-range supplementary immunization activities demonstrates that administration of YF vaccination with multi dose vials - even of larger presentation - could be effective if the aspects noted under wastage above are considered.

Since most opened vials of YF vaccine should be discarded 6 hours after opening or at the end of the immunization session (whichever comes first), use of fractional dose administration could increase wastage levels if the vaccine presentation is large. This is also borne out by estimations used for measles and rubella supplemental immunization activities, a lyophilised vaccine with similar handling characteristics post-reconstitution as YF vaccine.

The question of whether multiple septum piercings affects the integrity of the septum may need to be considered. YF vaccine contains no preservative and there is a potential risk of increased contamination if vials are repeatedly used (punctured) over the course of an immunization session. The use of lower dose vials would limit the number of punctures and might reduce the risk of contamination.^{xviii}

Communication strategy

The development of a funded communication strategy and proper messaging on the new delivery approach (or technology) would be crucial to ensure health worker and community acceptance. This strategy would need to be developed by the Ministry of Health with adequate lead time, and would need to clearly justify and explain the updated approach adopted for mass vaccination. It is essential that the health workforce and general population do not equate fractional dosing with achieving partial efficacy, as this could damage the credibility of the immunization programme well beyond YF vaccination.

Increased pain and swelling due to ID administration is a real risk, which as a consequence may lead to lower public acceptance, decreased trust and therefore lower coverage in certain communities. These risks can be addressed by adequate training but programme communications of what to expect are key to community acceptance. As a consequence, the communication strategy should include a component on crisis management and an effective response to adverse events that may occur following vaccination.

Health worker capacity building and training

All health personnel affected by the new strategy would need to be identified in order to be properly informed and adequately trained, particularly as this would be an "off label" use of the vaccine. Health workers will need to be properly informed on this aspect and more generally be trained on aspects related to YF mass vaccination campaigns^{xix}. Depending on the administration technique chosen (ID or

^{xviii} PATH is currently planning to conduct this type of testing for IPV vials (ID fIPV delivery) and potentially it could expand the testing to include yellow fever vials.

^{xix} http://apps.who.int/iris/bitstream/10665/156053/1/WHO_HSE_PED_CED_2015.1_eng.pdf?ua=1&ua=1, accessed June 2016

SC), appropriate training materials or guidance will have to be developed, which should also include all relevant aspects on safety and vaccine management, specifically adapted for the vaccine/manufacture of choice and to the injection device to be used. Training is needed for health workers to identify how to calibrate the correct dose, as similar type syringes may have more than one interpretable scale. If different syringes are supplied over time, this may create future confusion in the programme. Training and job aides should include all relevant aspects on vaccine handling, vaccination strategy and programme safety. Proper recording of vaccinations and monitoring should also be included in the training.

Adequate and sustained supervision would be essential for the successful implementation and monitoring of this approach and the activities should be properly included in the budget. As with any newly-introduced, unfamiliar practice, post-training support will be important and there will be a need to revise supervision instruments (tally sheets, monitoring forms may need to be adjusted) and develop feedback mechanisms. Supervision activities following initial training would need to be adequately planned and budgeted.

11. Surveillance and monitoring

Surveillance

When administering vaccination as a fractional dose within a campaign, individual vaccination records need to be established to allow for assessment of duration of protection, effectiveness, tracking of break-through cases and fractional dose vaccine safety (in particular rare SAE following immunization, such as neurotropic and viscerotropic disease) according to age and pending on how close to expiry date the vials are.

A YF Laboratory Network (YFLN) has been developed in the African Region on the backbone of the already existing Global Measles-Rubella Laboratory Network (GMRLN). Currently, 24 National YF laboratories have been established in 21 Member States of the African Region, mainly in countries at risk for YF outbreaks. These National Laboratories have been established predominantly in already existing National Measles-Rubella Laboratories to benefit from the investments made by WHO to establish these MR laboratories. Investments were made in capacity building (including training in conducting IgM testing, QA/QC, biosafety, laboratory management) as well as provision of essential equipment (ELISA washer and reader, automatic pipettes).

According to the YF case definition the diagnostic of a suspected case has to be confirmed by a positive genome detection (PCR) or the detection of YF specific IgM that negative for other flaviviruses (e.g., dengue, West Nile, or Zika viruses) through plaque reduction neutralization test (PRNT). Of note, YF specific IgM antibodies that are formed in response to infection with YF virus or YF vaccine virus cannot be differentiated with currently available rapid diagnostic tests. Furthermore, YF IgM can persist for

years following receipt of YF vaccine and therefore all suspect cases of YF vaccine should be asked about their previous history of YF vaccination in order to appropriately interpret the results.

WHO is working closely together with the Global Specialized Laboratory for YF at the Arbovirus laboratory, CDC-Fort Collins, who routinely provides the network with essential reagents to conduct YF IgM testing using a protocol developed by them and rolled out throughout the global laboratory network (LabNet). They also play a role in upgrading the expertise of individual laboratories and conduct referral testing, as well as quality assurance. A Regional Reference Laboratory for the African Region has been established at the Institut Pasteur of Dakar, Senegal. They provide confirmation of the results from national laboratories and further characterization of virus strains (IgM, IgG, virus isolation, molecular detection and characterization, virus neutralization) and QA/QC. This multi-tiered structure mimics both GMRLN and GPLN (Global Polio LabNet) in all aspects.

As part of the WHO guidance to the YFLN, WHO published a laboratory manual for YF diagnosis^{xx}. Throughout the last 15 years, WHO has organized several laboratory-training workshops to strengthen skills of the YF laboratory staff. Furthermore, annual YFLN meetings are conducted jointly with polio and measles networks to mutually benefit from each other's experience and highlight the integrated LabNet approach WHO is striving for.

Currently, efforts are underway to strengthen laboratory capacity for YF testing in countries not previously dealing with YF transmission, and considerations are made to establish additional RRLs to relieve the workload of IP Dakar.

The integrated approach of YF with polio and measles is also reflected in the integrated approach to YF surveillance.

Monitoring

A new guideline entitled Planning and Implementing High Quality Supplementary Immunization Activities for Measles-Rubella and other Injectable Vaccines has recently been developed.^{xxi} While this guideline uses measles-rubella vaccine as the example, the principles of campaign planning, implementation and monitoring can be applied to a mass vaccination campaign using YF vaccine. The new guidelines are intended for use by immunization programme managers and their partners and provide tools for use before (i.e., readiness assessment), during (i.e., rapid convenience monitoring) and after (i.e., rapid convenience monitoring and mopping up and coverage surveys) the campaign.

Recording vaccinations administered during campaigns on a vaccination card/home-based record is essential for the valid verification of immunization coverage during post-campaign surveys, and for establishing the total number of vaccine doses received by a child at school entry (where school enrolment screening policies exist). In particular for fractional dose use, personalized registries may prove useful when considering the need for with revaccination of full dose. Although the use of

^{xx} http://apps.who.int/immunization_monitoring/Manual_YF.pdf?ua=1, accessed June 2016

^{xxi} <http://www.who.int/immunization/diseases/measles/SIA-Field-Guide-revised.pdf?ua=1>, accessed June 2016

immunization cards can increase the campaign cost and workload, appropriate recording of every vaccination, fractional or full dose, (including those given during campaigns) is recommended by WHO.^{xxii} Training and supervision will need to constantly reinforce this issue because in many countries cards are not marked during Measles or Measles/Rubella Supplemental Immunization Activities or polio national immunization days. It is worth noting that a recorded receipt of a fractional dose does not qualify as YF certificate as per IHR.

12. Ethical considerations

In emergencies the international community has a collective duty of care to ensure that effective affordable measures are available to those most in need. The duty of care principle demands that effective vaccinations against disease threats should be available to those at risk. Emergencies often require rapid decision-making under uncertainty and unconventional measures, but ethical principles need to be adhered to even in these situations.

In the face of shortages, usually one strategy is prioritization among different population groups. The second is to use a “dose-sparing” approach in order to cover as much of the population as possible, of which the feasibility has been demonstrated by Wu et al. Both options could also be combined. The best of these options should be chosen based on a rigorous public health and ethical analysis.

There are a number of ethical issues that arise when choosing a «dose-sparing» approach:

Risk-benefit considerations

First, the risk of harm to populations and individuals needs to be analyzed («first do no harm principle»). These risks and possible mitigating actions to minimize them should be explicitly discussed. Second, there should be robust evidence for benefit, i.e. for the non-inferiority in comparison to the full dose. In addition, the “dose-sparing” strategy should be considered based on robust evidence for its benefit.

The obligation to produce and share data

In public health emergencies there is an ethical duty to produce and rapidly share all relevant data. The use of lower doses of vaccine as an emergency measure places an ethical obligation to learn as much as possible as quickly as possible. Even if the « dose-sparing » approach is not designed as a research project, research components should be embedded to use this opportunity to gain new knowledge. Ideally, protocols should be submitted for pre-approval now, so that final ethics review can be expedited.

Distributive Justice & Equity

Unless there is scientific necessity and evidence for doing so (e.g. based on safety or utility), the immunization programmes should not discriminate against any groups. Special measures should be taken to facilitate the access of vulnerable groups, such as children and pregnant women.

^{xxii} WHO Immunization, Vaccines and Biologicals: Home based records (available at http://www.who.int/immunization/monitoring_surveillance/routine/homebasedrecords/en/, accessed June 2016)

Transparency, trust, public engagement

The vaccination strategy should be well communicated by the national policy-makers to the public health officials, the public and the media. Special effort should be made to ensure that media understand well the rationale for the dose sparing and become real partners in disseminating the messages of the vaccine programmes. Public engagement will facilitate uptake and trust in the programme.

Informed consent

During mass vaccination campaigns, consent is normally presumed (implicit consent), with a possibility to opt-out. This means that information about the vaccine is disseminated widely in an accessible format, and it is ensured that the public knows that they can opt out of vaccination, if they so wish. If mass vaccination campaigns are being planned with the lower dose vaccine, it is an ethical requirement to provide minimum additional information: i.e. that a lower than usual dose will be used but that it is considered as safe and effective as the normal dose.

13. Recommendations

1. The use of YF fractional dose vaccination should be considered in response to an emergency situation in which current vaccine supply is insufficient. Fractional dose vaccination should be used for vaccination campaigns in response to an outbreak or in settings where the extension of the outbreak is imminent and should not be used for routine immunization. As soon as the vaccine supply situation normalizes, fractional dose should be replaced by full dose vaccination. Fractional dose vaccination is an off-label use of the product.
2. Under no circumstances should YF vaccine be reconstituted in different volume of diluent as recommended by the manufacturer, and no efforts should be undertaken to otherwise dilute the vaccine.
3. When YF vaccine is administered in fractional dose, preference should be given to the administration of the vaccine according to standard route, i.e. SC or IM. The minimal dose administered **should preferentially contain 3000 IU/dose, but no less than 1000 IU/dose and the minimum volume of administration should be not less than 0.1 ml.**
4. **The dose fractioning (e.g., ½ or 1/5th) should be done considering the potency of the vaccine batch, the shortage of supply and availability of suitable injection devices.**
5. In the absence of data on the use of fractional dose in young children, children below the age of 2 years should preferentially be offered a full dose of vaccine (i.e. 3000 IU or higher) during emergency campaigns.
- ~~6. Different expansion scenarios for YF vaccine fractional dose administration should be considered in view of the anticipated risk of the spread of the disease, and shortage in vaccine supply. Actual potencies of available vaccines need to be considered to meet potency levels as discussed before:~~

Note 9/2016:
Recommendation #6 was context specific in June 2016 and is no longer relevant

- ~~a. 1/2 dose of Biomanguinhos vaccine administered SC.~~
- ~~b. Should the shortage of vaccine exceed the use of ½ dose, use of a 1/5th dose of Biomanguinhos vaccine administered SC could be considered.~~
- ~~c. If the shortage even exceeds this fractional dose supply, all WHO prequalified vaccines could be administered as ½ or 1/5 th fractional dose SC, depending on potency of the batch. In such a context, use of Stamaril® (Sanofi) via ID administration (0.1 ml) is, while off label, also acceptable, depending on the preferences of the country. Generally use of fractionate doses should not go below the aforementioned minimal dose range (see recommendation 3).~~

7. **Reconstituted YF vaccine is heat labile and must be kept at 2-8°C at all times and discarded after 6 hours in accordance with WHO's open vial policy.**
8. No multi-dose vials containing more than 10 full doses should be used for fractional dose administration to reduce risk of contamination through multiple puncture of the septum.

9. All other precautions and recommendations for YF vaccination prevail as detailed in the WHO VPP.

10. Every effort must be made to monitor safety and YF vaccine AEFI's.

11. Vaccination with fractional dose should be recorded using personalized registries for purpose of safety and effectiveness monitoring. Such information could be useful in assessing eventual re-vaccination needs with full dose, for which currently there is no recommendation.

14. Research needs

The data appear sufficiently strong for emergency policy-decision making for the vaccines from 2 manufacturers (Sanofi Pasteur & Bio-Manguinhos) in relation to fractional dose administration of YF vaccine by ID and IM/SC route, respectively. However, to support a broader recommendation on fractional dose use of YF vaccine can be made, additional data should be generated and ideally all 4 WHO prequalified YF vaccine should be studied. Furthermore, since the data on fractional doses were generated in adult study populations, there is an urgent need to compile clinical trial data in children and infants. The specific research needs include:

- Immunological non-inferiority trials should be conducted comparing the full dose vs. a fractional dose of $\frac{1}{2}$ (0.25ml) and $\frac{1}{5}^{\text{th}}$ of the volume (0.1ml) using the same route of administration for all prequalified vaccines;
- Vaccine should include lots ex-factory and end of shelf-live, with recently measured potency expressed in IU.
- Studies should be conducted in healthy adults in *flavivirus*-naïve subjects, and with representative background of *flavivirus* pre-existing immunity, which should be duly characterized (dengue, YF, Zika, WNV in priority).
- An age de-escalation study should be conducted in children down to 9 months in order to assess immunogenicity.
- All studies should report baseline immune status, measure YF functional antibodies at 28 days and 12 months after vaccination using validated PRNT; viraemia (adults only), and safety and reactogenicity using standard procedures;
- Measures should be put in place for long-term follow up with of vaccinated subjects, and booster vaccination should be offered in case that titres fall below the protective threshold.

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YELLOW FEVER MASS VACCINATION CAMPAIGN USING FRACTIONAL DOSE IN KINSHASA, DRC

Background

In response to the ongoing yellow fever outbreak in neighbouring Angola and parts of the Democratic Republic of Congo (DRC), the Ministry of Health in DRC, with the support of WHO and other partners, conducted a mass vaccination campaign from 17 August - 5 September 2016 in 47 health zones (32 in Kinshasa, 15 along the border with Angola). In order to minimize transmission and reduce the chance of spread of the outbreak into the potentially vulnerable population of urban Kinshasa, the campaign targeted **all children over 9 months of age and all adults in urban Kinshasa** (a target population of **7,586,400**). Vaccination in Kinshasa took place over 10 days (17 August – 26 August).

Global supply of yellow fever vaccine is currently limited and in order to ensure that the entire target population of Kinshasa be vaccinated, the Ministry of Health in DRC opted for the use of a **partial or “fractional dose” approach** for the 32 health zones in Kinshasa. Children under 2 years (9 – 23 months) and pregnant women were offered a full dose of the vaccine. The inhabitants of the 15 health zones bordering Angola received full dose vaccination.

During the 10 days of vaccination activity in Kinshasa, **7,898,365** people were vaccinated, achieving an administrative coverage of 104%. Rapid convenience assessments (RCAs) reported an average vaccination coverage rate of 98.2% for all 32 health zones in Kinshasa.

Fractional dose

A fractional dose of yellow fever vaccine (0.1 ml) is one-fifth the volume of a standard yellow fever dose and is administered subcutaneously. Fractional doses are considered in light of the fact that WHO prequalified yellow fever vaccines can contain significantly more vaccine viral particles than the minimum requirement of 1000 IU/dose. Clinical trials studying safety and immunological non-inferiority of fractional dose of yellow fever vaccine demonstrate similar seroconversion and neutralizing antibody titres as with full dose.^{1,2,3,4}

Due to the constraints that the current yellow fever outbreaks are placing on the global stockpile of yellow fever vaccine, in June 2016 WHO reviewed the available data and recommended, in consultation with SAGE, that the use of fractional dose vaccination should be considered in response to an emergency situation in which current vaccine supply is insufficient.⁵ Given the absence of data on the use of fractional dose in young children, it was recommended that children below the age of 2 years should preferentially be offered a full dose of vaccine during emergency campaigns. The same applies to pregnant women.

Campaign planning and implementation

- 32 surveillance/medical/logistic/risk communication and community engagement/support staff from WHO were deployed to support the development of campaign microplans and to conduct pre-campaign training and monitoring.
- Existing microplans developed from previous yellow fever campaigns were adapted for the fractional yellow fever campaign in urban Kinshasa.
- A 1-day training session was organized to instruct all vaccination staff members supporting the fractional dose campaign on 15 August 2016.
- A press conference was held by the Ministry of Health on 10 August with the key press offices in Kinshasa to provide information about the campaign, including the use of fractional dose.
- Social mobilization for the campaign was conducted through proactive engagement of local television, print and radio media, posters, banners, microphone announcements and community mobilization, including interpersonal communication through door-to-door visits.
- Main messages were translated into four local languages.
- A total of **14,424** vaccinators supported implementation of the campaign.
- A total of **2,404** immunization posts were organized and operational over 10 days (Table 1) with 1 day for mop-up.
- Each team consisted a minimum of 5 vaccinators, 2 recorders, 1 social mobilizer/community engagement expert, and 1 volunteer to maintain order at the post, and 1 responsible for waste management.

Table 1. Numbers of vaccination sessions, total vaccinated with fractional and full dose, and median vaccinated per day and per session

Province	Kinshasa
Target population	7,586,400
No. campaign days	10
No. vaccination sessions conducted	24,040
No. vaccination posts	2,404
No. reported vaccinated (total)	7,898,365 (104% of target)
No. reported vaccinated (fractional dose)	7,466,998
No. reported vaccinated (full dose)	431,367
Median no. vaccinated per day	730,469

The yellow fever vaccines used in the Kinshasa campaign were 10 full-dose vials (5 ml per vial) manufactured by Bio-Manguinhos (Brazil) (2.5 million doses received), with 0.1 ml withdrawn for each fractional dose, and 0.5 ml drawn for every full dose vaccination. Therefore, each vial had the potential to contain up to 50 doses of vaccine. As yellow fever vaccine is lyophilized and without preservative, the multi-dose vial policy requires that reconstituted vials must be kept between +2°C and +8°C and must be used or discarded within 6 hours of opening, or at the end of the vaccine session, whichever comes first.⁶

Fractional doses (0.1 ml) were administered subcutaneously on the outer part of the right upper arm, using an autodisable syringe with 10-13 mm length needle. Full doses (0.5 ml) were administered to children 9-23 months and pregnant women, subcutaneously on the outer part of the right upper arm, using an autodisable syringe with a 16mm length needle.

After vaccination, each vaccine recipient was given a specially designed card indicating which dose (full or fractional) was received. The cards also included a disclaimer that the cards were not considered yellow fever vaccination certificates valid for international travel. Recipients were asked to report any adverse events occurring within a week of receiving the vaccine, including illness, hospitalizations or death.

19,416 safety boxes of waste were collected/destroyed during the Kinshasa campaign: 4,677 incinerated by MSF, 2,022 incinerated by Save the Children and 12,717 stored in the World Food Programme (WFP) warehouse, to be transported and incinerated at a central cement plant in Kinshasa.

AEFI surveillance

Since 2014, DRC has been involved in a process of strengthening the national system for monitoring Adverse Events Following Immunization (AEFI), culminating in June 2016 with the validation of a national manual for AEFI surveillance with clear identification of activities, actors and their roles and responsibilities. This campaign was an opportunity to launch the new AEFI surveillance system. An ad hoc committee was formed to steer the AEFI surveillance activities during the campaign, with membership from the Direction of Pharmacies (DPM), the National Centre of Pharmacovigilance (CNPV), the Expanded Programme on Immunization (EPI), the National Program for Emergency and Humanitarian Action (PNUAH) and the Provincial Division of Health (DPS) in Kinshasa. Information on AEFI was drawn from four main sources of information.

Through the passive surveillance system of DRC, as of 22 September, 123 AEFI were reported, of which 8 were serious. Among the reported AEFI, Kinshasa reported 78 cases of which 7 were serious (notification rate: 1 per 100,000 doses). Severe AEFI were followed up by investigations in three hospitals and seven mobile clinics. The results of the investigations are currently being analysed.

In addition to the passive surveillance system, an alert system to specifically report and follow up on severe AEFI was put in place in Kinshasa. 41 suspected serious AEFI were reported through this system.

A country-wide surveillance system that was put in place at the beginning of the epidemic to identify yellow fever cases detected 4 cases of yellow fever symptoms in people vaccinated during the preventive campaign in August 2016.

Finally, a community survey was led by the National Pharmacovigilance Centre to complement passive surveillance efforts. This survey yielded 4350 AEFI reports. The analysis of these reports is ongoing, but preliminary results as of 13 September indicate that from 1650 reports analysed, 500 have been classified as AEFI.

Campaign monitoring

32 WHO supervisors and 96 independent campaign monitors were assigned across 32 health zones in Kinshasa. A total of **2,404** vaccination sessions (1 visit to each post) were observed during the campaign. Supervisory checklists were modified to capture additional information unique to the fractional dose aspect of the campaign. Of over 350 supervisory checklists collected, data was consolidated from **335 reports** (the rest were rejected as incomplete).

According to the compiled reports, 96% of visited sites were well organized and full teams were present for 99% of sessions. Overall, the use of fractional doses was well understood by health workers (100%) and in 94% of sessions observed, fractional dose was administered correctly. In a few instances the health workers had difficulties with the use of the 0.1 ml syringes but this was corrected early in the campaign by supervisors. Injection safety was a concern as monitors reported seeing recapping of syringes in 24% of sessions observed. Monitors noted that despite multiple punctures to the vial septum, no leakage or bits of septum degradation/debris were observed in any of sessions. Average numbers of fractional doses able to be drawn from each vial were not accurately counted, as scoring errors resulted from overly busy sites and the combination of fractional and full dose delivery. However, an average wastage rate of only 3.2% (0.3% - 8.8%) was calculated overall.

Given the low thermostability of yellow fever vaccine following reconstitution, cold chain maintenance at the immunization sessions was a concern. In addition, the Bio-Manguinhos vials used in Kinshasa did not have VVMs attached. Only 31% of sites observed had a temperature monitor in the vaccine carrier. 89% of vaccine carriers observed had sufficiently cold ice packs and 84% of sites were correctly keeping the reconstituted vaccine vials in the foam cushion of the carriers. Diluent was sometimes kept out of the cold chain (6%). The multi-dose vial policy was properly adhered to in nearly all sites monitored. However, in 2 sites it was observed that reconstituted vials were put back in the refrigerator for use the following day. This was rapidly corrected by supervisors.

Fractional dosing (designated as “minimal dose”) was well understood by the population (97% of vaccine recipients questioned). However, health workers reported questions being raised on the duration of protection and on the validity for travel. Questions were also raised about vaccination of pregnant women as they have not been included in previous yellow fever vaccination campaigns. Correct messaging by health workers was observed in 95% of sites monitored. 9% of sites monitored reported having encountered cases of resistance to receiving the fractional dose, but 10% reported having encountered cases of resistance to the full dose as well.

As a result of a rumour circulating that yellow fever vaccine was incompatible with consumption of alcohol, lower attendance was observed at sites on the weekends. There were no widespread issues with false rumours or concerns specifically related to fractional dosing.

Post-campaign evaluation and coverage

A total of 7,898,365 people were reported to have been vaccinated during the campaign, representing 104% of the initially estimated target population. RCAs were conducted across 10,300 households representing 58,021 respondents. Of these, 56,974 (98%) reported being vaccinated during the campaign. Of the 2% not vaccinated, 21% (219/1,046) were reported as vaccine refusals. Reasons given for refusing the vaccine are presented in **Figure 1**.

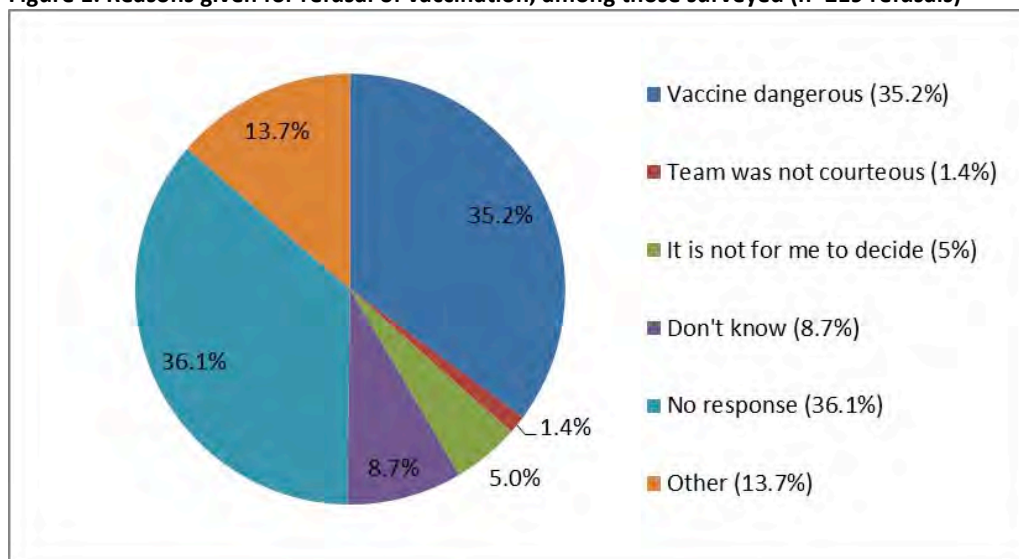
A full post-campaign assessment is currently underway, with a report expected by the end of October 2016.

Monitoring of immunity

The Yellow Fever partnership, under US CDC leadership in collaboration with the National Institute of Biomedical Research (INRB) in Kinshasa and WHO, launched a study that will assess immunogenicity at 28 days

and 12 months post vaccination. If the results of this study suggest poor immunogenicity, revaccination with a full dose will be considered.

Figure 1. Reasons given for refusal of vaccination, among those surveyed (n=219 refusals)



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Short-term research priorities for dose-sparing of YF vaccine

(Revised version 26 September 2016)

Context

To address an acute shortage of YF vaccine, a reactive vaccination campaign in response to a disease outbreak in Kinshasa, DRC Congo, was recently conducted using fractional dose of vaccine. This campaign was conducted following recommendations by WHO for the use of fractional-dose yellow fever vaccine as dose-sparing option. These recommendations are based on a limited number of clinical studies conducted on fractional dose administration of vaccine.

While the current scientific data support WHO's recommendation, important data gaps remain, such as fractional-dose performance in infants, applicability to all WHO-prequalified vaccines, and persistence of neutralizing antibody. Some of this information can be obtained in the near term, while other information would require long-term follow up. The priorities listed below focus on the most important short term objectives.

Answering these questions may permit broadening and also possibly simplification of WHO's recommendations on fractional dose use in case of need for emergency campaigns.

Research questions*

Question to be addressed	Proposed study	Study details
Can all WHO-prequalified YF vaccines be administered SC using fractional dose approach?	Immunological non-inferiority trial in adults comparing fractional dose to standard dose of all four WHO-prequalified vaccines.	Blood sampling at baseline and ~4 weeks post-vaccination to measure neutralizing antibodies by PRNT**; viraemia testing, potentially in a subset of vaccinees (blood or urine).
Is fractional dose vaccination sufficiently immunogenic in infants?	Immunological non-inferiority trial comparing fractionate dose to standard dose in children down to 9 -12 months of age.	Blood sampling at baseline and ~4 weeks post-vaccination to measure neutralizing antibodies by PRNT.
Is the long-term immunity affected by the reduced dose?	Long-term immunological assessments of fractional dose recipients (explore feasibility of clinical trial cohort from Biomanguinhos)***	Blood sampling \geq 1 year post-vaccination (e.g. 1y, 2.5y, 5y) to measure neutralizing antibodies by PRNT.
Is immune response to YF fractional dose comparable across different genetic backgrounds?	Proposed study should include as 1 st priority populations from Sub-Saharan Africa, as 2 nd priority populations from East Asia (India, China).	Consider different regions in Sub-Saharan Africa.

Is fractional dose vaccination sufficiently immunogenic in individuals with HIV infection (CD4 counts >200 cells/ μ l)?	Immunological non-inferiority trial comparing full dose to fractionate dose in immunocompromised HIV infected subjects.	Blood sampling at baseline and ~4 weeks post vaccination to analyze for neutralizing antibodies by PRNT.
Is there increased incidence of severe AEFI following vaccination with a fractional dose compared to a standard dose?	Close monitoring during the vaccination campaign up to 1 month post vaccination.	Documentation of side effects and further evaluation of serious adverse events (vaccine-associated neurotropic and viscerotropic disease, AND and AVD).

* As WHO's recommendation is potency, and not volume based, all above studies should be normalized by actual vaccine potency, or, if not feasible, be conducted on a representative batch of vaccine. The design of all studies should include representative sampling of males and females.

**PRNT = Plaque reduction neutralization test.

*** Recognizing that immune response in volunteers may be influenced by exposure to other flaviviruses