



**World Health
Organization**

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

SAGE

April 2017

**Strategic Advisory Group of Experts
on Immunization
25 - 27 April 2017**

**Executive Boardroom
WHO HQ, Geneva**



**World Health
Organization**

SAGE April 2017

This booklet contains key background documents for the
meeting of the
Strategic Advisory Group of Experts (SAGE) on immunization
25 - 27 April 2017

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

[SAGE/meetings/2017/April](https://www.who.int/sage/meetings/2017/April)

Table of Contents – April 2017 SAGE meeting

Agenda.	1
List of SAGE members.	6
SAGE Terms of References.	8
Current SAGE Working Groups.	18
Provisional list of participants.	25
Session 1: Report from IVB Director.	
1. Meeting of the Strategic Advisory Group of Experts on immunization, October 2017 – conclusions and Recommendations. WER No. 48, 2016.	46
2. SAGE tracking record of recommendations and action points.	68
3. Summary World Immunization Week 2017, 24-30 April 2017.	95
4. Report of the AFRO Regional Immunization Technical Advisory Group Meeting, 12-13 December 2016, Dakar, Senegal.	96
5. Declaration on universal access to immunization as a cornerstone for health and development in Africa, African Union, 2016.	132
6. 2016 progress report Immunization Demand Team. Vaccine-Preventable Diseases programme (VPI), EURO.	133
7. Fifth hepatitis B immunization experts resource panel consultation, 15-17 February 2017, Manila, Philippines.	150
Session 2: Report from Gavi, the Vaccine Alliance.	
1. Update on the Gavi Board meeting 02–03 December 2016.	157
Session 3: Report from other Advisory Committees on Immunization.	
1. Global Advisory Committee on Vaccine Safety (GACVS), 30 November-01 December 2016. WER No 2, 2017.	158
2. Immunization in Practices Advisory Committee (IPAC) revised terms of reference.	166
3. Executive Summary. Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC) summary of conclusions and recommendations, Veyrier du Lac, France, 01-02 February 2017.	174
Session 4: Polio eradication initiative.	
1. Thirteenth Meeting of the SAGE Polio Working Group (WG) WHO, Geneva, February 09-10, 2017, Geneva– notes from the meeting.	180
2. Should countries continue IPV vaccination in their routine immunization programme after the certification of polio eradication? If so, what is the optimum schedule and for how long should countries continue? Evidence to recommendation table.	190
3. Grassly NC., Immunogenicity and Effectiveness of Routine Immunization With 1 or 2 Doses of Inactivated Poliovirus Vaccine: Systematic Review and Meta-analysis. The Journal of Infectious Diseases, 2014.	204
Session 5: Oral Cholera Vaccines.	
1. Background Paper on Whole-Cell, Killed, Oral Cholera Vaccines without appendices (full version on the SAGE website).	212
Session 6: Ebola Vaccines.	
1. Update with the development of Ebola vaccines and implications to inform future policy recommendations: prepared by the Ebola Working Group.	287
2. Henao-Restrepo AM et al., Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised	321

trial (Ebola Ça Suffit!). The Lancet, 2017.	
Session 7: The Immunization manager of the Decade of Vaccines (leadership, capacity building, good practices).	
1. CDC GID Immunization Competencies Project. Competencies of the Immunization Technical Workforce. National Level. Draft.	335
Session 8: Strengthening of National Immunization Technical Advisory Groups (NITAGs).	
1. National Immunization Technical Advisory Groups Background Paper.	350
Session 9: Engagement of private immunization providers.	
1. Levin A and Kaddar M, Role of the private sector in the provision of immunization services in low- and middle-income countries. Health Policy Planning, 2011	391
2. Mitrovich R, et al., A Review of the Private Sector's Contribution to Immunization Service Delivery in Low, Middle, and High-Income Countries.	400
3. WHO Guidance Note: Engagement of Private Providers in immunization service delivery. Considerations for National Immunization Programmes. Draft.	425
Session 10: Diphtheria.	
1. Review of the epidemiology of diphtheria – 2000-2016.	448
2. Systematic review on diphtheria vaccine effectiveness and immunogenicity.	483
3. Supply of diphtheria antitoxin.	503



Agenda

**Meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization
25 - 27 April 2017
Executive Board Room, WHO Headquarters, Geneva, Switzerland**

Tuesday, 25 April 2017

Time	Session	Purpose of session, target outcomes and questions for SAGE	Duration
9:00	Welcome – introduction of participants A. Cravioto, Chair of SAGE.		20 min.
9:20	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
10:20	Coffee/Tea break	Break	30 min.
10:50	Report from Director, IVB – Session 1, contd. Discussion contd.		
11:50	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.
12:30	Lunch	Break	1h 30 min

14:00	<p>Reports from other Advisory Committees on Immunization – Session 3</p> <p>Global Advisory Committee on Vaccine Safety (GACVS). R. Pless, Chair of GACVS. 10 min.</p> <p>Discussion: 10 min.</p> <p>Immunization Practice Advisory Committee (IPAC). C. Morgan, Chair of IPAC. 10 min.</p> <p>Discussion: 10 min.</p> <p>Expert Committee on Biological Standardization (ECBS). K. Cichutek, Chair of ECBS. 10 min.</p> <p>Discussion: 10 min.</p> <p>Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC). R. Breiman, Chair of IVIR-AC. 20 min.</p> <p>Discussion: 20 min.</p>	<p>FOR INFORMATION</p>	1h 40 min.
<p>15:40</p> <p>16:10</p>	<p>Coffee/tea break</p> <p>Polio eradication initiative - Session 4</p> <p>Update of Global Polio Eradication Initiative. M. Zaifran, WHO. 30 min.</p> <ul style="list-style-type: none"> ▪ WPV and cVDPV2 elimination ▪ Other objectives in the GPEI Strategy Plan (2013-18) <p>Updates on IPV supply landscape. D. Chang-Blanc, WHO, A. Ottosen, UNICEF. 20 min.</p> <p>Discussion: 40 min.</p> <p>Report from SAGE Polio WG. Y. AL-Mazrou, Chair of the Polio WG. 30 min.</p> <ul style="list-style-type: none"> ▪ Assessment of progress towards WPV and cVDPV2 elimination ▪ Benefit of IPV in WPV eradication, cVDPV2 outbreak and routine immunization ▪ Recommendations on future immunization policy <p>Discussion: 60 min.</p>	<p>Break</p> <p>FOR INFORMATION AND DISCUSSION</p> <p>This session will include an update on progress of the polio eradication initiative and a discussion on the future immunization policy after the full OPV withdrawal from the routine schedule.</p> <p>To inform and update SAGE on the:</p> <ul style="list-style-type: none"> • Current status of the polio eradication program. • IPV supply situation. • Biocontainment of poliovirus. • Transition planning (Post Certification Strategy). <p>To ask for SAGE's recommendation on:</p> <ul style="list-style-type: none"> • Role of IPV in eliminating WPV, outbreak response to cVDPV and routine immunization. • Future IPV immunization policy after the global certification (e.g. duration of the IPV use, IPV schedule). 	<p>30 min.</p> <p>3h</p>
19:10	End of Day		
19:15	Cocktail		

Wednesday, 26 April 2017

8:30	<p>Use of oral cholera vaccines - Session 5</p> <p>Overview of the global cholera situation. D. Legros, WHO, 15 min.</p> <p>Discussion: 10 min.</p> <p>Presentation on evidence of vaccine effectiveness and safety across different settings and age groups. F. Luquero, Epicentre, 20 min.</p> <p>Discussion: 30 min.</p> <p>Conclusions of the SAGE Working Group on oral cholera vaccines and proposed recommendations. A. Cravioto, SAGE and Chair of WG on oral cholera vaccines, 15 min.</p> <p>Discussion: 30 min.</p>	<p>FOR DECISION</p> <p>SAGE will be presented with a report of the SAGE working group on oral cholera vaccines and expected to provide recommendations on the use of oral cholera vaccines with particular focus on cholera endemic settings, humanitarian crisis and on the control of cholera outbreaks.</p> <p>The SAGE recommendations will then be reflected in an updated WHO vaccine position paper on the use of cholera vaccines with a target publication date of Q3 2017.</p>	2h
10:30	<p>Coffee/tea break</p>	<p>Break</p>	30 min.
11:00	<p>Ebola vaccines Update with the development of Ebola vaccines and implications to inform future policy recommendations - Session 6</p> <p>Introduction to the session. F. Were, Co-Chair of the Ebola WG, 5 min.</p> <p>Overview of Ebola epidemiology D. Heymann, Public Health England and Chattam House, 10 min. (Via teleconference)</p> <p>Update on Ebola candidate vaccines R&D plans, immunogenicity, efficacy and safety and timelines for licensure. G. Disbrow, US Biomedical Advanced Research and Development Authority, TBC, 10 min.</p> <p>Observed and forecasted impact of different candidate Ebola vaccines immunization strategies and target populations. A. Camacho, London School of Hygiene and Tropical Medicine and Epicentre, 10 min.</p> <p>Access to Ebola vaccines before licensure and after licensure. M. Serafini, Médecins Sans Frontières Switzerland, 10 min.</p> <p>Conclusions. H. Rees, Co- Chair of the Ebola WG, 10 min.</p> <p>Discussion: 1 h 5 min.</p>	<p>FOR INFORMATION AND DECISION</p> <p>For information</p> <p>Present SAGE with data on immunogenicity, efficacy, effectiveness and safety of candidate Ebola vaccines and, on the observed and projected impact of different vaccination strategies using compassionate use data and from mathematical models.</p> <p>For decision</p> <p>Request SAGE's recommendations on the following:</p> <ul style="list-style-type: none"> • Are there remaining challenges that may prevent access to Ebola vaccines in future outbreaks, and if yes can SAGE make recommendations on how these might be addressed. • Is the current evidence sufficient for SAGE to make recommendations regarding the use of Ebola vaccines (e.g. rVSV and the Russian vaccine) in case of another Ebola outbreak (pre-licensure and/or post licensure)? <ul style="list-style-type: none"> -If yes, which recommendations can be proposed? -If not, what key data are missing? 	2h
13:00	<p>Lunch</p>	<p>Break</p>	1h

14:00	<p>National immunization programme management: functions and competencies - Session 7</p> <p>Introduction, importance, and ongoing initiatives. J. Jawad, SAGE Member, 10 min.</p> <p>Challenges in performing expected programme management functions: country presentations:</p> <p>Pakistan, S. Gilani, EPI National Programme Manager, Ministry of Health, 15 min.</p> <p>Armenia, G. Sahakyan, National Immunization Programme Manager, Ministry of Health, 15 min.</p> <p>Functions and competencies needed at the national level. D. Traicoff, US Centers for Disease Control and Prevention, 10 min.</p> <p>Normative guidance to strengthen immunization programme management functions: proposed activities and process. J. Bahl, WHO, 10 min.</p> <p>Discussion: 1 hr.</p>	<p>FOR INFORMATION AND DISCUSSION</p> <p>Inform SAGE of the current ongoing initiatives related to the defining of functions and competencies expected from immunization programme management and their strengthening.</p> <p>Present SAGE with challenges in performing the required programme management functions.</p> <p>SAGE will be requested to provide feedback on WHO and partner activities in framing normative guidance normative guidance on functions and competencies expected from a national immunization programme and supporting countries in implementing them.</p>	2h
16:00	Coffee/tea break	Break	30 min.
16:30	<p>Strengthening of National Immunization Technical Advisory Groups (NITAGs) - Session 8</p> <p>Progress achieved, L. Dumolard, WHO, 10 min.</p> <p>Successes, issues and challenges in establishing, strengthening and sustainability of NITAGs.</p> <p>United Kingdom, A. Pollard, SAGE member and Chair of Joint Committee on Vaccination and Immunisation, 10 min.</p> <p>Sri Lanka, P. Mahipala, WHO and previously Chair of Sri Lanka NITAG, 10 min.</p> <p>Senegal, A. Dia Tal, Chair of Senegal NITAG, 10 min.</p> <p>Partners' support to countries, successes and challenges, lessons learnt and future plans. N. MacDonald, SAGE member, 20 min.</p> <p>Discussion: 1 hr.</p>	<p>FOR INFORMATION AND DISCUSSION</p> <p>To update SAGE on:</p> <ul style="list-style-type: none"> o Progress achieved in the establishment and strengthening of NITAGs (as per GVAP goals). o Successes, issues and challenges that countries are facing in establishing and strengthening their NITAGs, including needs of the country, importance of the NITAG and its sustainability. o Partners' support to countries, successes and challenges, lessons learnt and future plans. <p>To request SAGE's guidance to ensure that the GVAP NITAGs 2020 goals are achieved and that NITAGs are contributing to the improvement of national immunization programmes.</p>	2h
18:30	End of day		

Thursday, 27 April 2017

08:30	<p>Private providers engagement with immunization programmes - Session 9</p> <p>Introduction to the session, issues and definitions. N. Turner, SAGE member, 10 min.</p> <p>Systematic review of issues related to the engagement of private providers, M. Watkins, US CDC, 15 min.</p> <p>Engagement of private providers with the national Immunization programme: opportunities and challenges. Country experiences. India, S. Zodpey, Public Health Foundation of India, 10 min. Uganda, H. Luzze, Ministry of Health, 10 min.</p> <p>Discussion: 30 min.</p> <p>Proposed recommendations for the engagement of the private sector and steps to facilitate, effective relationships to improve immunization coverage and quality services and reduce equity gaps. N. Turner, SAGE member, 15 min.</p> <p>Discussion: 30 min.</p>	<p>FOR INFORMATION AND DISCUSSION</p> <p>Present SAGE with the range and complexity of models of private providers engagement in health care services.</p> <p>Present SAGE with considerations related to the engagement of private providers with immunization services and the implementation of National Immunization Programmes: contributions, risks, challenges and roadblocks.</p> <p>Identify drivers of effective engagement of the private providers with the National Immunization Programme.</p> <p>Present SAGE with draft guidance to support optimization of engagement with private providers and request input on recommendations to countries in order to improve coverage and quality of vaccine delivery and reduce equity gaps.</p> <p>Request SAGE's input on next steps at the international level and how to facilitate collaboration between the private and the public sector to support the goals of the GVAP.</p>	2h
10:30	Coffee/tea break	Break	30 min.
11:00	<p>Diphtheria - Session 10</p> <p>Review of data from recent diphtheria outbreaks. K. Clark, US Centers for Disease Control and Prevention, 15 min.</p> <p>Questions: 10 min.</p> <p>Review of serological/immunogenicity/effectiveness data. M. Marti, WHO, 15 min.</p> <p>Questions: 10 min.</p> <p>Availability of diphtheria anti-toxin. M. Friede, WHO, 15 min.</p> <p>Questions: 10 min.</p> <p>Conclusions and recommendations. K. Johansen, SAGE member, 10 min.</p> <p>Discussion: 35 min.</p>	<p>FOR INFORMATION AND DECISION</p> <p>SAGE will be presented with an analysis of recent diphtheria outbreaks as well as with a systematic review on the duration of protection of diphtheria vaccination.</p> <p>SAGE will be asked to decide whether there is sufficient evidence to revisit the recommendation on the administration of decennial diphtheria booster doses to adults and synchronization of schedules in light of the recently revised position papers on pertussis and tetanus vaccines. The aim will be to lead to an updating of the 2006 diphtheria vaccine WHO position paper.</p> <p>SAGE will further be informed of the current status of diphtheria antitoxin supply and plans to ensure availability.</p>	2h
13:00	Closing		20 min.
13:20	End of meeting		

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

SAGE members

<p>Dr Rakesh Aggarwal Professor Department of Gastroenterology Sanjay Gandhi Postgraduate Institute of Medical Sciences 226014 Lucknow India</p>
<p>Dr Yagob Yousef Al-Mazrou Secretary General Council of Health Services Riyadh 12628 Saudi Arabia</p>
<p>Dr Alejandro Cravioto SAGE Chair Facultad de Medicina Universidad Nacional Autónoma de México 04318 Coyoacan 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 Jee, Youngmee Director Center for Immunology and Pathology Korean CDC Cheongju Republic of Korea</p>
<p>Dr Kari Johansen SAGE-Vice Chair 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 Noni MacDonald Professor of Pediatrics Division Pediatric Infectious Diseases Dalhousie University B3K 6R8 Halifax, Nova Scotia Canada</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>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 form as per the attached form (Annex 1).

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 (Annex 2).

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

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.

Version: 09 Feb. 2016

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 3 (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/).

DECLARATION OF INTERESTS FOR WHO EXPERTS

WHO's work on global health issues requires the assistance of external experts who **may have interests related to their expertise**. To ensure the highest integrity and public confidence in its activities, WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to a potential conflict of interest related to the subject of the activity in which they will be involved.

All experts serving in an advisory role must disclose any circumstances that could represent a **potential conflict of interest** (i.e., any interest that may affect, or may reasonably be perceived to affect, the expert's objectivity and independence). You must disclose on this Declaration of Interest (DOI) form any financial, professional or other interest relevant to the subject of the work or meeting in which you have been asked to participate in or contribute towards and any interest that could be affected by the outcome of the meeting or work. You must also declare relevant interests of your immediate family members (see definition below) and, if you are aware of it, relevant interests of other parties with whom you have substantial common interests and which may be perceived as unduly influencing your judgement (e.g. employer, close professional associates, administrative unit or department).

Please complete this form and submit it to WHO Secretariat if possible at least 5 weeks before the meeting or work. You must also promptly inform the Secretariat if there is any change in this information prior to, or during the course of, the meeting or work. All experts must complete this form before participation in a WHO activity can be confirmed. Please note that not fully completing and disclosing all relevant information on this form may, depending on the circumstances, lead WHO to decide not to appoint you to WHO advisory bodies / functions in the future.

Answering "Yes" to a question on this form does not automatically disqualify you or limit your participation in a WHO activity. Your answers will be reviewed by the Secretariat to determine whether you have a conflict of interest relevant to the subject at hand. One of the outcomes listed in the next paragraph can occur depending on the circumstances (e.g. nature and magnitude of the interest, timeframe and duration of the interest).

The Secretariat may conclude that no potential conflict exists or that the interest is irrelevant or insignificant. If, however, a declared interest is determined to be potentially or clearly significant, one or more of the following three measures for managing the conflict of interest may be applied. The Secretariat (i) allows full participation, with public disclosure of your interest; (ii) mandates partial exclusion (i.e., you will be excluded from that portion of the meeting or work related to the declared interest and from the corresponding decision making process); or (iii) mandates total exclusion (i.e., you will not be able to participate in any part of the meeting or work).

All potentially significant interests will be **disclosed** to the other participants at the start of the activity and you will be asked if there have been any changes. Whereas this form is confidential, a summary of declarations and actions taken to manage any declared interests will be **published** on the SAGE public website). Furthermore, if the objectivity of the work or meeting in which you are involved is subsequently questioned, the contents of your DOI form may be made available by the Secretariat to persons outside WHO if the Director-General considers such disclosure to be in the best interest of the Organization, after consulting with you. Completing this DOI form means that you agree to these conditions.

If you are unable or unwilling to disclose the details of an interest that may pose a real or perceived conflict, you must disclose that a conflict of interest may exist and the Secretariat may decide that you be totally recused from the meeting work or process concerned, after consulting with you.

Name: Institution: Email:

Date and title of meeting or work, including description of subject matter to be considered (if a number of substances or processes are to be evaluated, a list should be attached by the organizer of the activity):

Please answer each of the questions below. If the answer to any of the questions is "yes", briefly describe the circumstances on the last page of the form.

The term "you" refers to yourself and your immediate family members (i.e., spouse (or partner with whom you have a similar close personal relationship) and your children). "Commercial entity" includes any commercial business, an industry association, research institution or other enterprise whose funding is significantly derived from commercial sources with an interest related to the subject of the meeting or work. "Organization" includes a governmental, international or non-profit organization. "Meeting" includes a series or cycle of meetings.

EMPLOYMENT AND CONSULTING

Within the past 4 years, have you received remuneration in excess of US\$ 5,000 from a commercial entity or other organization with an interest related to the subject of the meeting, work or process?

- 1a Employment Yes No
- 1b Consulting, including service as a technical or other advisor Yes No

RESEARCH SUPPORT

Within the past 4 years, have you or has your research unit received support from a commercial entity or other organization with an interest related to the subject of the meeting, work or process?

- 2a Research support, including grants, collaborations, sponsorships, and other funding Yes No
- 2b Non-monetary support valued at more than US \$1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc.) Yes No
- 2c Support (including honoraria) for being on a speakers panel, giving speeches or training for a commercial entity or other organization with an interest related to the subject of the meeting, work or process? Yes No

INVESTMENT INTERESTS

Do you have current investments (valued at more than US\$5,000 overall) in a commercial entity with an interest related to the subject of the meeting, work or process? Please also include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds or similar investments that are broadly diversified and on which you exercise no control.

- 3a Stocks, bonds, stock options, other securities (e.g., short sales) Yes No
- 3b Commercial business interests (e.g., proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company) Yes No

INTELLECTUAL PROPERTY

Do you have any intellectual property rights that might be enhanced or diminished by the outcome of the meeting, work or process?

- 4a Patents, trademarks, copyrights or other intellectual property (including pending applications) Yes No
- 4b Proprietary know-how in a substance, technology or process Yes No

PUBLIC STATEMENTS AND POSITIONS (during the past 4 years)

- 5a As part of a regulatory, legislative or judicial process, have you provided an expert opinion or testimony, related to the subject of the meeting, work or process, for a commercial entity or other organization? Yes No
- 5b Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of the meeting, work or process? Yes No

ADDITIONAL INFORMATION

- 6a If not already disclosed above, have you worked for the competitor of a product that is the subject of the meeting or work, or will your participation in the meeting, work or process enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial or business competitive advantage? if so, please elaborate? Yes No
- 6b To your knowledge, would the outcome of the meeting, work or process benefit or adversely affect interests of others with whom you have substantial common personal, professional, financial or business interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)? Yes No
- 6c Excluding WHO, has any person or entity paid or contributed towards your travel costs in connection with this WHO meeting, work or process? Yes No
- 6d Have you received any payments (other than for travel costs) or honoraria for speaking publicly on the subject of this WHO meeting, work or process? Yes No
- 6e Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence? Yes No

TOBACCO OR TOBACCO PRODUCTS (answer without regard to relevance to the subject of the meeting or work)

Within the past 4 years, have you had employment or received research support or other funding from, or had any other professional relationship with, an entity directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity? Yes No

EXPLANATION OF "YES" RESPONSES: If the answer to any of the above questions is "yes", check above and briefly describe the circumstances on this page. If you do not describe the nature of an interest or if you do not provide the amount or value involved where relevant, the conflict will be assumed to be significant.

Nos. 1 - 4: Type of interest, question number and category (e.g., Intellectual Property 4.a copyrights) <u>and</u> basic descriptive details.	Name of company, organization, or institution	Belongs to you, a family member, employer, research unit or other?	Amount of income or value of interest (if not disclosed, is assumed to be significant)	Current interest (or year ceased)
Nos. 5-8: Describe the subject, specific circumstances, parties involved, time frame and other relevant details				

CONSENT TO DISCLOSURE. By completing and signing this form, you consent to the disclosure of any relevant conflicts to other meeting participants and in the resulting report or work product.

DECLARATION. I hereby declare on my honour that the disclosed information is true and complete to the best of my knowledge.

Should there be any change to the above information, I will promptly notify the responsible staff of WHO and complete a new declaration of interest form that describes the changes. This includes any change that occurs before or during the meeting or work itself and through the period up to the publication of the final results or completion of the activity concerned.

Date: _____

Signature _____



CONFIDENTIALITY UNDERTAKING

1. Commercial, academic and other research institutions and individual scientists often submit or present for discussion by committees or groups of WHO on research, products and processes (hereafter referred to as "Information") which the institutions and individuals consider proprietary. To help ensure the appropriate use by WHO of such Information whilst protecting the institutions' or individual's proprietary rights, WHO undertakes to release such Information only to persons who have signed this agreement.
2. Information submitted by such institutions or individuals through WHO to committees or groups for review, discussion or comment, whether at meetings, on internet-based collaborative workspaces, during telephone conferences or otherwise, shall be regarded by the Undersigned as confidential, unless clearly stated otherwise, by the institution, individual concerned and/or the WHO Secretariat.
3. The Undersigned undertakes to treat such confidential Information as proprietary information and agrees not to make copies of it, nor to disclose or use the same in whole or in part.
4. If requested to do so, the Undersigned agrees to return to WHO any and all Information identified as confidential.
5. The Undersigned shall not be bound by confidentiality if he/she is able to demonstrate that the Information:
 - (a) was known to him/her prior to any disclosure to him/her by the institution or individual or WHO;
 - (b) was in the public domain at the time of disclosure by the institution or individual;
 - (c) becomes part of the public domain through no fault of the Undersigned; or
 - (d) becomes available to the Undersigned from a third party not in breach of any legal obligations of confidentiality to the institution, individual or WHO.
6. This Confidentiality Undertaking is valid during the entire time the Undersigned participates in the work of the committee or group, in whatever capacity, and for a period of ten (10) years thereafter.

Signed:

Signature.....

Name.....
(print or type)

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 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 being determined by the Working Group Chair, Lead WHO technical staff and SAGE Executive secretary based on the contribution of the member to the group. If some members resign for personal reasons, are no longer eligible to serve on the group, 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 below). 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.

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 for 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. From the pool of nominees, the Working Group Chair, SAGE Executive Secretary and Lead WHO staff will propose a Working Group composition for endorsement by the SAGE Chair and the Director of the Department of Immunization, Vaccines and Biologicals. The proposed list should be accompanied by the rationale for the proposed selection. In addition to meeting the required expertise, attention will be given to ensure proper diversity including geographic and gender representation. Chairs of regional technical immunization advisory groups are not eligible to serve on SAGE Working Groups.

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.

Version: 09 Feb. 2016

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 decision 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 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 will establish a telephone bridge for the teleconferences and ensure 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. 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.

Version: 09 Feb. 2016

Working Groups are encouraged to submit publications of the reviews of the scientific evidence in 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. Summarized Declarations of Interest are 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. The posted summary will then 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:
 - 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).
 - 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.
 - 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;
 - 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:
 - Policy and programmatic options for the use of different OPV formulations and IPV delivery options, and
 - 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)
- Youngmee Jee: Korean Centre for Disease Control and Prevention, Republic of Korea. (Member of the Working Group from October 2016)

Experts

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

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

Terms of Reference

- Review progress towards global measles control targets and regional measles and rubella elimination goals and highlight key obstacles.
- 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 vaccines (including outbreak response immunization) and surveillance strategies.
- 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 other relevant technical advisory committees (e.g. Immunization and vaccines related implementation research advisory committee (IVIR-AC), and the Immunization Practice Advisory Committee (IPAC)) to address relevant quantitative issues as well as those related to immunization practices.
- Explore the potential use of new technologies that could help improve coverage and thereby expedite elimination of measles/rubella.
- Advise SAGE, no later than 2020, whether a formal global goal for measles eradication and/or rubella eradication should be set with timeframes for its achievement.

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)
- Jaleela Sayed Jawad, Ministry of Health, Kingdom of Bahrain (Member of the Working Group since January 2017, SAGE Member since 2015).
-

Experts

- 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 (Member of the Working Group since November 2011).
- David Durrheim: Hunter New England Area Health Service, Australia (Member of the Working Group since November 2011, SAGE Member 2009 - 2012).
- Mark Jit, London School of Hygiene and Tropical Medicine, UK (Member of the Working Group since January 2017)
- Susan Reef: Centers for Disease Control and Prevention, United States of America (Member of the Working Group since November 2011).
- Helen Rees: University of Witwatersrand, South Africa. (former SAGE Chair 2010 - 2013)
- William Moss: Johns Hopkins University, United States of America.
- Walter Orenstein, Emory University School of Medicine, USA (Member of the Working Group since January 2017)

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

Updated: April 2017

SAGE Members

- Narendra Arora: International Clinical Epidemiology Network, India. (Chair of the Working Group and SAGE member until April 2016)
- Yagob Al-Mazrou: Health Services Council, Saudi Arabia.
- Alejandro Cravioto: Faculty of Medicine of the Universidad Nacional Autónoma de México (UNAM), Mexico.

Experts

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

- Nick Andrews: Public Health England, United Kingdom.
- George Bonsu: Ministry of Health, Ghana.
- David Durrheim: Hunter New England Area Health Service, Australia. (SAGE member until April 2012)
- Ann Kelly: University of Exeter, United Kingdom.
- Jesse Goodman: Georgetown University, United States of America (resigned from Working Group in January 2017).
- Jean-Paul Jemmy: Médecins Sans Frontières, Belgium.
- Keymanthri Moodley: Stellenbosch University, South Africa.
- Cesar Velasco Muñoz: Hospital Clínico Lozano Blesa, Spain.

- Diop Ndack: University Cheikh Anta Diop, Senegal.
- Chris Ockenhouse: PATH, United States of America.
- Helen Rees: University of Witwatersrand, South Africa. (Co-Chair of the Working Group and former SAGE Chair 2010 - 2013)
- Oyewale Tomori: Redeemer's University, Nigeria. (Co-Chair of the Working Group until March 2016 and SAGE member until April 2015)

Ex-Officio members

- Chris Morgan: Chair of WHO Immunization Practices Advisory Committee (IPAC).
- K. Cichutek: 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 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: Faculty of Medicine of the Universidad Nacional Autónoma de México (UNAM), Mexico (Chair of the Working Group).
- Firdausi Qadri: International Centre for Diarrhoeal Disease Research, Bangladesh.
- Jaleela Sayed Jawad: Ministry of Health, Bahrain.

Experts

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

6. 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

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

7. 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.

Updated: April 2017

8. SAGE Working Group on the use of bacille Calmette-Guérin vaccine (established October 2016)

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 bacille Calmette-Guérin (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 tuberculosis (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);
5. Assessment of the duration of protection and need for revaccination (including a comparison of the effect of revaccination with that of alternative protective approaches e.g. isoniazid preventive therapy);
6. 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);
7. 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);
8. 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, including BCG improvement strategies that may have implications for beneficial non-specific vaccine effects of the current BCG. The vaccine has several non-specific effects (NSE) which should be discussed but which should not be the immediate focus of the Working Group since this issue of NSE is being address by the Immunization and Vaccines-Related Implementation Research Advisory Committee (IVIR-AC).

Composition

SAGE Members

- Charles Shey Wiysonge: South African Medical Research Council, South Africa (Chair of the Working Group)
- Kari Johansen: European Centre for Disease Prevention and Control, Sweden

Experts

- Safaa Al-Khawaja: Ministry of Health, Bahrain
- Pamela Bakkabulindi: Ministry of Health, Uganda
- Sang Nae Cho: Yonsei University College of Medicine, South Korea
- Nigel Curtis: University of Melbourne, Australia
- Mark Hatherill: University of Cape Town, South Africa
- Guangxue He: Chinese Center for Disease Control and Prevention, China
- Helen McShane: University of Oxford, England
- Elizabeth Obimbo: University of Nairobi, Kenya
- Jeffrey Starke: Baylor College of Medicine, USA

9. SAGE Working Group on pneumococcal conjugate vaccine (established December 2016)

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.

Composition

SAGE Members

- Andrew J. Pollard: University of Oxford, United Kingdom (Chair of the Working Group)
- Kate O'Brien: Johns Hopkins Bloomberg School of Public Health, United States of America

Experts

- Narendra Arora: The INCLEN Trust International, New Delhi
- Stefan Flasche: London School of Hygiene & Tropical Medicine, United Kingdom
- Kyung-Hyo Kim: Ewha Womans University School of Medicine, Republic of Korea
- David Goldblatt: University College London, United Kingdom
- Elisabeth Lieke Sanders¹: National Institute for Public Health and the Environment, The Netherlands
- Dafrossa Lyimo: Ministry of Health, Tanzania
- Elizabeth Miller: Public Health England, United Kingdom
- Edward Kim Mulholland: Murdoch Childrens Research Institute, Australia
- Tamara Pilishvili: Centers for Disease Control and Prevention, United States of America
- Betuel Sigauque: Manhica Health Research Centre, Mozambique
- Cristiana Toscano: Federal University of Goiás, Brazil

**Strategic Advisory Group of Experts (SAGE) on Immunization
25 - 27 April 2017
Executive Board Room, WHO/HQ, Geneva, Switzerland**

Provisional list of participants as of 04 April 2017

SAGE Members

<p>Aggarwal, Rakesh Professor Department of Gastroenterology Sanjay Gandhi Postgraduate Institute of Medical Sciences 226014 Lucknow India</p>
<p>Al-Mazrou, Yagob Yousef Secretary General Saudi Health Council 3161-13315 Riyadh Saudi Arabia</p>
<p>Cravioto, Alejandro SAGE Chair Facultad de Medicina Universidad Nacional Autónoma de México 04318 Coyoacan Mexico</p>
<p>Jani, Ilesh Director General Instituto Nacional de Saúde Maputo Mozambique</p>
<p>Jawad, Jaleela Head of immunization group Public Health Directorate Ministry of Health Manama Bahrain</p>
<p>Jee, Youngmee Director Center for Immunology and Pathology Korean Center for Disease Control and Prevention Cheongju Republic of Korea</p>
<p>Johansen, Kari SAGE Vice-Chair European Center for Disease Control and Prevention 11A171 Solna Sweden</p>
<p>MacDonald, Noni Professor of Pediatrics Division Pediatric Infectious Diseases Dalhousie University B3K 6R8 Halifax, Nova Scotia Canada</p>
<p>Nolan, Terry Head Melbourne School of Population and Global Health The University of Melbourne 3010 Carlton Australia</p>

<p>O'Brien, Kate Professor International Health Johns Hopkins Bloomberg School of Public Health 21231 Baltimore United States of America</p>
<p>Pollard, Andrew J. Professor of Paediatric Infection and Immunity and Honorary Consultant Paediatrician Department of Paediatrics University of Oxford OX3 9DU Oxford United Kingdom of Great Britain and Northern Ireland</p>
<p>Qadri, Firdausi Temporary Advisers Senior Director Infectious Diseases Division International Centre for Diarrhoeal Disease Research, Bangladesh 1212 Dhaka Bangladesh</p>
<p>Shey Wiysonge, Charles Director South African Cochrane Centre South African Medical Research Council 7505 Cape Town South Africa</p>
<p>Turner, Nikki Associate Professor General Practice and Primary Care University of Auckland 6012 Wellington New Zealand</p>
<p>Were, Fredrick Dean School of Medicine University of Nairobi 00202 Nairobi Kenya</p>

Chairs of Regional Technical Advisory Groups

<p>Figuerola, Peter Chair, PAHO TAG Department of Community Health & Psychiatry University of the West Indies Kingston 7 Jamaica</p>
<p>Finn, Adam Chair, EURO TAG University of Bristol BS2 8AE Bristol United Kingdom of Great Britain and Northern Ireland</p>
<p>Hall, Robert Chair, WPRO TAG Senior Lecturer, School of Public Health and Preventive Medicine Monash University 3004 Melbourne Australia</p>
<p>Kang, Gagandeep Chair, SEARO TAG Professor and Head, Division of Gastrointestinal Sciences Christian Medical College 632004 Vellore India</p>

Rees, Helen
Chair, AFRO TAG
Executive Director
Wits Reproductive Health and HIV Institute
2001 Johannesburg
South Africa

Chairs of other WHO Immunization Advisory Groups

Breiman, Robert
Chair, IVIR-AC
Emory University
30322 Atlanta
United States of America

Cichutek, Klaus
Chair, ECBS
Director
Paul-Ehrlich-Institut
63225 Langen
Germany

Kaslow, David
Chair, PDVAC
Vice President
Essential Medicines
Program for Appropriate Technology in Health (PATH)
98121 Seattle
United States of America

Morgan, Christopher
Chair, IPAC
Head, International Development
Maternal and Child Health Program
Macfarlane Burnet Centre for Medical Research and Public Health
3004 Melbourne
Australia

Pless, Robert
Chair, GACVS
Public Health Agency of Canada
K1A 0K9 Ottawa
Canada

Representative of Missions in Geneva

Clasen, Annika
German Mission to the UN, Geneva
Geneva
Switzerland

Lathuille, Ariane
Health Attaché
French Mission to the UN, Geneva
1292 CHAMBESY
Switzerland

Nishizawa, Hideaki
Japanese Mission to the UN, Geneva
Geneva
Switzerland

Nolan, Canice
Minister Counsellor
Delegation to the UNOG
European Union
1211 Geneva
Switzerland

<p>Romeu, Belkis Third Secretary Cuban Mission to the UN, Geneva 1292 Geneve Cuba</p>
<p>Schmitz Guinote, J. H. German Mission to the UN, Geneva 1209 Genève Switzerland</p>
<p>Sierra, Patricia Chacon Special Assistant Monaco Mission to the UN, Geneva 1209 Geneva Switzerland</p>
<p>Zand, Niloofar Senior Advisor, Health and Nutrition Canadian Mission to the UN, Geneva 1202 Geneva Switzerland</p>
<p>de Moura Gomes, Juliana Second Secretary Health Brazilian Mission to the UN, Geneva 1202 Geneve Switzerland</p>

Other Registered Participants

<p>Afridi, Hameed Director - EPI Health Dept. of Health, Govt. of Khyber Pakhtunkwha Peshawar Pakistan</p>
<p>Aguado de Ros, M. Teresa Independent vaccines and immunization consultant 1290 Versoix Switzerland</p>
<p>Ahrendts, Johannes Head of Strategy Gavi, the Vaccine Alliance 1202 Geneve Switzerland</p>
<p>Andrews, Ross Chair of the Australian Technical Advisory Group on Immunisation (ATAGI) Epidemiologist Global and Tropical Health Division Menziess School of Health Research 4000 Spring Hill Australia</p>
<p>Ba-Nguz, Antoinette Regional Coordinator SIVAC Initiative Agence de Médecine Préventive (AMP) 656-0606 NAIROBI Kenya</p>
<p>Bachy, Catherine Vaccination advisor Medical Médecins sans Frontières (MSF) 1050 Brussels Belgium</p>

<p>Baloch, Shakir Provincial Manager Health EPI Balochistan 87300 Quetta Pakistan</p>
<p>Bergsaker, Marianne A.R. Senior Medical Officer Department of Vaccines Norwegian Inst. of Public Health 0403 Oslo Norway</p>
<p>Berraud, Orianne Program Associate Center for Vaccine, Innovation and Access Program for Appropriate Technology in Health (PATH) 1218 Le Grand Saconnex Switzerland</p>
<p>Berthels, Nele clinical assessor vaccines Federal Agency for Medicines and Health Products 1060 Brussels Belgium</p>
<p>Beyene, Endale Immunization Technical Advisor United States Agency for International Development (USAID) 22202 Arlington United States of America</p>
<p>Bhutta, Tariq Chairman NITAG Lahore Pakistan</p>
<p>Biellik, Robin Consultant Epidemiologist 1278 La Rippe Switzerland</p>
<p>Bijleveld, Pascal Director, Country Support Country Program Gavi, the Vaccine Alliance Geneva Switzerland</p>
<p>Bonvehí, Pablo Chair National Immunization Technical Advisory Board Argentina C1414COB Ciudad Autonoma de Buenos Aires Argentina</p>
<p>Breggi, Gianluca Managing Director Fondazione Achille Sclavo 53100 Siena Italy</p>
<p>Brown, Susan Director, Public Policy Engagement Gavi, the Vaccine Alliance 1202 Geneva Switzerland</p>

<p>Buanga-Lembwadio, Mireille Programme Officer Country Support Gavi, the Vaccine Alliance 1202 Geneva Switzerland</p>
<p>Camacho, Anton Epicentre 75012 Paris France</p>
<p>Chobanyan, Anna head Chief of Intensive Therapy Department Surb Astvatsamayer 0039 Yerevan Armenia</p>
<p>Clados, Mirjam Senior Executive Officer Country Programmes Gavi, the Vaccine Alliance Geneva Switzerland</p>
<p>Clarke, Kristie Medical Epidemiologist Global Immunization Division U.S. Centers for Disease Control and Prevention 30329 Atlanta United States of America</p>
<p>Cochi, Stephen Senior Advisor Global Immunization Division U.S. Centers for Disease Control and Prevention 30329 Atlanta United States of America</p>
<p>Cohen, Olivia International Vaccine Access Center Johns Hopkins Bloomberg School of Public Health 21231 Baltimore United States of America</p>
<p>Cronin, Anne Senior Partners' Engagement Framework Manager Policy Funding and Strategy Gavi, the Vaccine Alliance 1202 Geneva Switzerland</p>
<p>Deehan, Heather Chief, Vaccine Centre Supply Division United Nations International Children's Emergency Fund (UNICEF) 2150 Nordhavn Denmark</p>
<p>Dellepiane, Nora Consultant 1270 Trélex Switzerland</p>
<p>Derrough, Tarik European Centre for Disease Prevention and Control (ECDC) Expert Vaccine Preventable Diseases European Centre for Disease Prevention and Control 17165 Solna Sweden</p>

<p>Dietterich, Amy (Marion) Gavi CSO Constituency Coordinator Health Department International Federation of Red Cross and Red Crescent Societies 1214 Vernier Switzerland</p>
<p>Dochez, Carine Director, Network for Education and Support in Immunisation (NESI) Epidemiology and Social Medicine University of Antwerp 2610 Antwerp Belgium</p>
<p>Dong, Shaozhong Deputy Director of IMBCAMS Institute of Medical Biology, Chinese Academy of Medical Sciences 650118 Kunming The People's Republic of China</p>
<p>Douba, Alfred Assistant Professor Public Health Universite Felix Houphouet Boigny Abidjan Cocody Abidjan Côte d'Ivoire</p>
<p>Ducomble, Tanja Vaccine working group leader medical Médecins Sans Frontières (MSF) 1201 Geneva Switzerland</p>
<p>Edmunds, John Epidemiology & Population Health London School of Hygiene and Tropical Medicine WC1E 7HT London United Kingdom of Great Britain and Northern Ireland</p>
<p>Elder, Greg Medical Director Access Campaign Médecins Sans Frontières (MSF) CH 1211 Geneva Switzerland</p>
<p>Essoh, Tene-Alima Regional Director Africa Support to EPI/New Vaccines introduction /Vaccine safety programme Agence de Médecine Préventive (AMP) Abidjan Côte d'Ivoire</p>
<p>Feavers, Ian Head of Division Bacteriology NIBSC EN6 3QG Potters Bar United Kingdom of Great Britain and Northern Ireland</p>
<p>Feletto, Marta Senior Technical Officer Policy Access and Introduction, Centre for Vaccine Innovation and Access Program for Appropriate Technology in Health (PATH) 1218 Geneva Switzerland</p>
<p>Feng, Zijian Chinese Center for Disease Control and Prevention Beijing The People's Republic of China</p>

<p>Folly, Yann Gavi Secretariat focal point for Polio session Sr Prog Manager IPV, Penta Vaccine Implementation Gavi, the Vaccine Alliance 1202 Genève Switzerland</p>
<p>Gilani, Makhdoomzada Syed Saqlain Ahmad Observer to share the changes in EPI Pakistan National Programme Manager Expanded Programme on Immunization EPI Expanded Programme on Immunization EPI 44000 Islamabad Pakistan</p>
<p>Gouya, Mohammad Mehdi Director General Iranian Center for Communicable Diseases Control (CDC) Iranian Ministry of Health & Medical Education Tehran Iran (Islamic Republic of)</p>
<p>Grais, Rebecca Epicentre 75011 Paris France</p>
<p>Hadler, Stephen Deputy Director, Division of Bacterial Diseases National Center for Immunization and Respiratory Diseases U.S. Centers for Disease Control and Prevention 30333 Atlanta United States of America</p>
<p>Hamadeh, Randa Sami EPI Manager, Head PHC Expanded Programme on Immunization Ministry of Public Health Beirut Lebanon</p>
<p>Henaff, Louise Knowledge Manager Agence de Médecine Préventive (AMP) 75012 Paris France</p>
<p>Henkens, Myriam International Médical Coordinateur International Office Médecins Sans Frontières (MSF) B1050 Brussels Belgium</p>
<p>Heymann, David Present by videoconference from London the epidemiology of Ebola Professor London School of Hygiene and Tropical Medicine SW3 3RP London United Kingdom of Great Britain and Northern Ireland</p>
<p>Hounkanrin, Ginette Programme Officer HPID Agence de Médecine Préventive (AMP) Ouagadougou Burkina Faso</p>

<p>Howard, Natasha Asst Professor GHD London School of Hygiene and Tropical Medicine (LSHTM) WC1H 9SH London United Kingdom of Great Britain and Northern Ireland</p>
<p>Kallenberg, Judith Head of Policy Gavi, the Vaccine Alliance 1202 Geneve Switzerland</p>
<p>Karrar, Zaielabdin Abdelrahim Abdelrahman Cairperson, NITAG Sudan President Sudan Medical Council 11111 Khartoum Sudan</p>
<p>Kayembe Ntumba, Jean-Marie Dean School of Medicine University of Kinshasa Kinshasa Democratic Republic of the Congo</p>
<p>Khatib-Othman, Hind Managing Director Country Programmes Gavi, the Vaccine Alliance 1202 Geneva Switzerland</p>
<p>Kim, Min-Kyung observer Epidemic Intelligence Service Officer Division of VPD control and NIP Korean Center for Disease Control and Prevention 28159 Chungju-si Republic of Korea</p>
<p>Ko, Melissa Gavi, the Vaccine Alliance Geneva Switzerland</p>
<p>Kumar, Raj Gavi, the Vaccine Alliance Geneve Switzerland</p>
<p>Lambert, Paul-Henri ADVAC University of Geneva 1290 Versoix Switzerland</p>
<p>Laxamana, Maria Francia Observer DEPARTMENT OF HEALTH Manila Philippines</p>
<p>Levine, Orin Director, Vaccine Delivery Global Development Bill & Melinda Gates Foundation 98102 Seattle United States of America</p>

<p>Lim, Yen-Hong Clinton Health Access Initiative (CHAI) Boston United States of America</p>
<p>Lindstrand, Ann Head of Unit Monitoring and surveillance at Unit of Vaccinationprograms The Public Health Agency of Sweden SE_17182 Solna Sweden</p>
<p>Longini, Ira Professor University of Florida 32601 Gainesville United States of America</p>
<p>Lorenzo, David Managing Director Policy Access and Introduction Program for Appropriate Technology in Health (PATH) Geneva Switzerland</p>
<p>Lucas, Gilberto Member of Mozambique's Immunizations Experts Commite (CoPI) Ministry of Health 264 Maputo Mozambique</p>
<p>Luquero, Francisco Speaker Epicentre 1202 Geneva Switzerland</p>
<p>Luzze, Henry Deputy Manager Expanded Programme for Immunization (EPI) Ministry of Health Kamplala Uganda</p>
<p>Lynch, Julia Deputy Director General Development & Delivery Unit International Vaccine Institute(IVI) 151-919 Seoul Republic of Korea</p>
<p>Madrid, Yvette Consultant 1205 Geneve Switzerland</p>
<p>Malhame, Melissa Head, Market Shaping Policy and Market Shaping Gavi, the Vaccine Alliance 1202 Geneva Switzerland</p>
<p>Malvolti, Stefano Managing Director MMGH Consulting 8049 Zürich Switzerland</p>

<p>Mantel, Carsten Immunitization / Infectious Disease Epidemiology Robert Koch Institute 13353 Berlin Germany</p>
<p>Martinez, Lindsay Consultant Versoix Switzerland</p>
<p>Martinez Garcia, Daniel Paediatric & Vaccination Adviser Medical Department Médecins Sans Frontières (MSF) 1211 Geneva Switzerland</p>
<p>Matzger, Helen Bill & Melinda Gates Foundation Seattle United States of America</p>
<p>Menan, Hervé Director Biology CeDReS CHU de Treichville 1775 Abidjan Côte d'Ivoire</p>
<p>Mengel, Martin Coordinator - African Cholera Surveillance Network Enteric Diseases Agence de Médecine Préventive (AMP) 75015 Paris France</p>
<p>Miller, Mark Associate Director for Research, Director, Division of International Epidemiology and Population Studies Fogarty International Center National Institutes of Health 20892 Bethesda, MD 20892 United States of America</p>
<p>Mok, Wilson Gavi, the Vaccine Alliance 1202 Geneva Switzerland</p>
<p>Mongbo, Mèdessi Yves Armand To participate and also to share WAHO experience in establishing and strengthening NITAGs in the ECOWAS Region PO Child Adolescent Youth and Erderly Health Primary Health Care West African Health Organisation (WAHO) BOBO-DIOULASSO Burkina Faso</p>
<p>Mounier-Jack, Sandra Currently working on SIVAC-NITAG evaluation Associate Professor GHD London School of Hygiene and Tropical Medicine WC1H 9SH London United Kingdom of Great Britain and Northern Ireland</p>
<p>Mugali, Raveesha Participant Senior Manger HSIS Gavi, the Vaccine Alliance 1202 Geneva Switzerland</p>

<p>Muhammed, Amina Abdul-One Secretariat ,Nigerian Immunization Technical Advisory Group Medical officer Disease Control And Immunization National Primary Health Care Development Agency 900247 Abuja Nigeria</p>
<p>Nandy, Robin Principal Advisor & Chief of Immunizations Health Section/Programme division United Nations International Children's Emergency Fund (UNICEF) 10017 New york United States of America</p>
<p>Neels, Pieter Vaccine Advice BVBA 2980 Zoersel Belgium</p>
<p>Nguyen, Aurelia Director, Policy & Market Shaping Policy & Performance Gavi, the Vaccine Alliance 1202 Geneva Switzerland</p>
<p>Nickels, Emily Senior Consultant Linksbridge SPC 98109 Seattle United States of America</p>
<p>Nokleby, Hanne Chief Scientific Adviser Norwegian Institute of Public Health 0403 Oslo Norway</p>
<p>Okojie, Obehi Professor Department of Community Health University of Benin Benin-City Nigeria</p>
<p>Olivé, Jean-Marc Self Lochau Austria</p>
<p>Ortega-Perez, Inmaculada Senior Project Associate Agence de Médecine Préventive (AMP) 75015 Paris France</p>
<p>Ottosen, Ann Senior Manager Supply Division, Vaccine Centre United Nations International Children's Emergency Fund (UNICEF) 2150 Copenhagen Denmark</p>
<p>Pagliusi, Sonia DCVMN International Nyon Switzerland</p>

<p>Patel, Deepali Senior Programme Officer Policy & Performance Gavi, the Vaccine Alliance 1202 Geneva Switzerland</p>
<p>Peisley, Hope Director, Immunisation Policy Section Immunisation Branch, Office of Health Protection Department of Health 2606 Woden Australia</p>
<p>Puumalainen, Taneli Chief Physician, Head of Vaccination Programme Unit Finnish National Institute for Health and Welfare FI-00271 Helsinki Finland</p>
<p>Sagar, Karan Senior Country Manager Country Support Gavi, the Vaccine Alliance 1202 Geneva Switzerland</p>
<p>Sahakyan, Gayane National Immunization Program Manager NITAG Secretary Ministry of Health 0047 Yerevan Armenia</p>
<p>Salvati, Anna Laura Agenzia Italiana del Farmaco Rome Italy</p>
<p>Samoilovich, Elena Head of Laboratory Laboratory of Vaccine-Preventable Diseases Republican Research and Practical Center for Epidemiology and Microbiology 200114 Minsk Belarus</p>
<p>Sandhu, Hardeep Team Lead Workforce Development Team CDC Atlanta Centers for Disease Control and Prevention, USA Decatur United States of America</p>
<p>Schemionek, Katja Participant Senior Specialist HSIS Gavi, the Vaccine Alliance 1202 Geneva Switzerland</p>
<p>Schluter, W. William Director Global Immunization Division CDC 30029 Atlanta United States of America</p>
<p>Setayesh, Hamidreza Senior Country Manager Country Support Gavi, the Vaccine Alliance 1202 Geneva Switzerland</p>

<p>Shen, Angela Senior Advisor, USAID US Government 20201 Washington DC United States of America</p>
<p>Steinglass, Robert Director Immunization Center John Snow, Inc. (JSI) 22209 Arlington United States of America</p>
<p>Sternin, Sam Gavi, the Vaccine Alliance Geneva Switzerland</p>
<p>Stuart, James London School of Hygiene and Tropical Medicine London United Kingdom of Great Britain and Northern Ireland</p>
<p>Tal Dia, Anta President of senegalese NITAG Executive Director Institut de sante et developpement University Cheikh Anta Diop Dakar Senegal</p>
<p>Theopold, Nicolas Senior Manager, Strategy Gavi, the Vaccine Alliance Geneva Switzerland</p>
<p>Thion, Chloé Agence de Médecine Préventive (AMP) 75015 Paris France</p>
<p>Tiwari, Tejpratap Medical Epidemiologist Meningitis and Vaccine Preventable Diseases Branch U.S. Centers for Disease Control and Prevention 30329-4027 Atlanta United States of America</p>
<p>Traicoff, Denise PH Training Specialist Global Immunization Division U.S. Centers for Disease Control and Prevention 30333 Atlanta United States of America</p>
<p>Tsehay, Yemane Berhane Director Addis Continental Institute of Public Health Addis Ababa Ethiopia</p>
<p>Valentiner-Branth, Palle Head of VPD section, MD PhD Department of infectious disease epidemiology and prevention Statens Serum Institut DK-2300 Copenhagen S Denmark</p>

<p>Vilajeliu, Alba Senior Programme Officer Gavi, the Vaccine Alliance Geneva Switzerland</p>
<p>Vizzotti, Carla Secretary Sociedad Argentina de Infectologia 1085 Ciudad Autonoma de Buenos Aires Argentina</p>
<p>Wang, Susan Associate Director for Research & Implementation Science Global Immunization Division U.S. Centers for Disease Control and Prevention 30333 Atlanta United States of America</p>
<p>Watkins, Margaret Epidemiologist Global Immunization Division U.S. Centers for Disease Control and Prevention 30333 Atlanta United States of America</p>
<p>Weller, Charlie Wellcome Trust London United Kingdom of Great Britain and Northern Ireland</p>
<p>Wichmann, Ole Director Immunization Unit Robert Koch Institute 13353 Berlin Germany</p>
<p>Yeraliyeva, Lyazzat Chair of National Consultation Committee on immunization Associated Professor Children Infectious Disease Kazakh National Medical University 050000 Almaty Kazakhstan</p>
<p>Zodpey, Sanjay Invited Speaker Vice President- Academics Academics Public Health Foundation of India 122002 Gurgaon India</p>
<p>da Silva, Alfred Executive Director Agence de Médecine Préventive (AMP) 75015 Paris France</p>
<p>de Gabrielli, Albane Gavi, the Vaccine Alliance Geneva Switzerland</p>

Industry

<p>Barbosa, Paula Vaccines Policy Manager Vaccines IFMA 1202 Geneva Switzerland</p>
<p>Bardone, Corinne Head of Global Public Affairs for PPH and Corporate Campaigns Public Affairs for Vaccines Sanofi Pasteur 69007 Lyon France</p>
<p>Benson, Joan Executive Director Program Partnerships Merck & Co. Inc. 19486 West Point United States of America</p>
<p>Bigger, Laetitia Director Vaccines Policy IFPMA 1211 Geneva Switzerland</p>
<p>Bijlwan, Divya Vice President Strategic Operations and Planning Biological E Limited Hyderabad India</p>
<p>Datla, Mahima Managing Director MD Office Biological E Limited 500033 Hyderabad India</p>
<p>Faircloth, Kyra Director Public Affairs PFIZER Inc. 10017 NY United States of America</p>
<p>Fletcher, Mark Andrew Africa & Middle East Medical Lead Pfizer Vaccines PFIZER Inc. 75014 Paris France</p>
<p>Fukushi, Hiromichi Associate Manager Clinical Development & Regulatory Affairs Department, Research and Development Division Kitasato DaiichiSankyo Vaccine Co., Ltd. 140-8710 Tokyo Japan</p>
<p>Gao, Yongzhong General Manager Xiamen Innovax Biotech Co.,Ltd. 361022 Xiamen The People's Republic of China</p>

<p>Glück, Reinhard Chief Scientific Officer Member of the Executive Committee Zydus Cadila Healthcare Ltd. 382213 Changodar, Ahmedabad India</p>
<p>Harshavardhan, G.V.J.A Director Viral Vaccines & International Affairs Bharat Biotech Int. imited 500 078 Hyderabad India</p>
<p>Ivol, Sabrina Janssen Vaccines & Prevention B.V. Leiden Netherlands</p>
<p>Jadhav, Suresh Executive Director Quality Assurance & Regulatory Affairs Serum Institute of India Pvt. Ltd. 411028 Pune India</p>
<p>Lobos, Fernando Director Business Development Director Business Development Sinergium Biotech S.A B1619IEA Garín Argentina</p>
<p>Meurice, Francois Ambassador Vaccines Scientific Affairs and Public Health GlaxoSmithKline (GSK) 1300 Wavre Belgium</p>
<p>Millogo, Jules Director, International Organizations Merck Vaccine Merck 19454 North Wales United States of America</p>
<p>Morgan, Lyn observer Head of Global Public Affairs for Endemic Vaccines, Institutions, & Associations Public Affairs Sanofi Pasteur 69007 Lyon France</p>
<p>Poonawalla, Cyrus Chairman & Managing Director Serum Institute of India Pvt. Ltd. 411028 Pune, Maharastra 411028 India</p>
<p>Prasad, Sai D. President Quality Operations Bharat Biotech International Limited 500 078 Hyderabad India</p>

<p>Rae, Logan Senior Director Government Affairs , Vaccines Business Unit Medical Affairs Takeda Pharmaceuticals International GmbH 8152 Glattpark- Opfikon Switzerland</p>
<p>Reers, Martin Head Technical operations BE Vaccines 44800 Saint Herblain France</p>
<p>Shinoda, Kaori R&D Planning & Management Department Kitasato Daiichi Sankyo Vaccine Co., Ltd. 364-0026 Kitamoto-shi Japan</p>
<p>Spreng, Simone Regulatory Affairs Janssen Vaccines Switzerland 3018 Bern Switzerland</p>
<p>Tippoo, Patrick Head, Science and Innovation Science and Innovation The Biovac Institute 7405 Cape Town South Africa</p>
<p>Tsai, Theodore Policy Scientific Affairs Takeda Vaccines 02139 Cambridge United States of America</p>
<p>Yang, Lingjiang DCVMN EC member Manager International Business and Cooperation CNBG Chengdu Institute of Biological Products Co., Ltd. 610023 Chengdu The People's Republic of China</p>
<p>Youn, Hyunjun(David) Manager Vaccine Division LG Chem 03184 Seoul Republic of Korea</p>

WHO/HQ and Regional staff

<p>Bahl, Jhilmil World Health Organization Immunization, Vaccines and Biologicals/EPI</p>
<p>Bahl, Sunil WHO Regional Office for South-East Asia (SEARO) Family Health, Gender and Life Course</p>
<p>Banerjee, Kaushik World Health Organization Immunization, Vaccines and Biologicals, IVB/EPI</p>
<p>Benassi, Virginia World Health Organization Immunization, Vaccines & Biologicals, IVB/IVR</p>

<p>Bloem, Paulus J. World Health Organization Immunization, Vaccines and Biologicals, IVB/EPI</p>
<p>Butler, Robb Regional Adviser, EURO Programme Manager, Vaccine Preventable Diseases and Immunization (VPI)</p>
<p>Cernuschi, Tania World Health Organization Immunization, Vaccines & Biologicals, IVB/EPI</p>
<p>Chang Blanc, Diana World Health Organization Immunization, Vaccines and Biologicals, IVB/EPI</p>
<p>Chaudhri, Irtaza WHO Regional Office for Eastern Mediterranean (EMRO) Vaccine Preventable Diseases & Immunization, EM/VPI</p>
<p>Cherian, Thomas World Health Organization Immunization, Vaccines and Biologicals, IVB/EPI</p>
<p>Cohen, Adam World Health Organization Immunization, Vaccines and Biologicals, IVB/EPI</p>
<p>Costello, Anthony World Health Organization Maternal, Newborn, Child and Adolescent Health, FWC/MCA</p>
<p>Dabbagh, Alya Jaafar World Health Organization Immunization, Vaccines and Biologicals, IVB/EPI</p>
<p>Danovaro, Carolina World Health Organization Immunization, Vaccines and Biologicals, IVB/EPI</p>
<p>Diorditsa, Sergey WHO Regional Office for the Western Pacific (WPRO) Expanded Programme for Immunization (EPI)</p>
<p>Doren, André World Health Organization Polio Eradication Initiative, POL</p>
<p>Duclos, Philippe World Health Organization Immunization, Vaccines and Biologicals, IVB/DO</p>
<p>Dumolard, Laure World Health Organization Immunization, Vaccines and Biologicals/EPI</p>
<p>Finkernagel, Malin World Health Organization Immunization, Vaccines and Biologicals, IVB/DO</p>
<p>Furrer, Eliane World Health Organization Immunization, Vaccines and Biologicals, IVB/IVR</p>
<p>Gacic-Dobo, Marta World Health Organization Immunization, Vaccines and Biologicals, IVB/EPI</p>
<p>Giersing, Birgitte World Health Organization Immunization, Vaccines and Biologicals, IVB/EPI</p>

<p>Goodman, Tracey S. World Health Organization Immunization, Vaccines and Biologicals, IVB/EPI</p>
<p>Grevendonk, Jan World Health Organization Immunization, Vaccines and Biologicals, IVB/EPI</p>
<p>Gsell, Pierre World Health Organization Immunization, Vaccines and Biologicals, IVB/IVR</p>
<p>Harutyunyan, Vachagan World Health Organization Polio Eradication, POL/SSC</p>
<p>Hasan, Hayatee World Health Organization Immunization, Vaccines and Biologicals, IVB/DO</p>
<p>Hombach, Joachim Maria World Health Organization Immunization, Vaccines and Biologicals, IVB/IVR</p>
<p>Hutubessy, Raymond World Health Organization Immunization, Vaccines and Biologicals, IVB/IVR</p>
<p>Kirorei Corsini, Catherine World Health Organization Immunizations, Vaccines and Biologicals, IVB/DO</p>
<p>Kretsinger, Katrina World Health Organization Immunization, Vaccines, and Biologicals, IVB/EPI</p>
<p>Mahipala, Palitha WHO Regional Office for Eastern Mediterranean (SEARO) Noncommunicable Diseases and Env Health</p>
<p>Marti, Melanie World Health Organization Immunization, Vaccines and Biologicals, IVB/DO</p>
<p>Menning, Lisa World Health Organization Immunization, Vaccines and Biologicals, IVB/EPI</p>
<p>Mihigo, Richard Regional Adviser on Immunization (AFRO) Programme Area Coordinator, Immunization and Vaccine-Preventable Diseases</p>
<p>Mihretu, Belete World Health Organization Expanded Programme on Immunization (EPI)</p>
<p>Mulders, Mick World Health Organization Immunization, Vaccines and Biologicals, IVB/EPI</p>
<p>Okwo-Bele, Jean-Marie World Health Organization Immunization, Vaccines and Biologicals, IVB/DO</p>
<p>Patel, Minal World Health Organization Immunization, Vaccines, and Biologicals, IVB/EPI</p>
<p>Petit, Dörte World Health Organization Immunization, Vaccines and Biologicals, IVB/EPI</p>

<p>Preziosi, Marie-Pierre World Health Organization Immunization, Vaccines and Biologicals, IVB/IVR</p>
<p>Ramirez Gonzalez, Alejandro World Health Organization Immunization, Vaccines and Biologicals, IVB/EPI</p>
<p>Riveros, Ximena World Health Organization Immunization, Vaccines and Biologicals, IVB/IVR</p>
<p>Ruiz Matus, Cuauhtemoc WHO Regional Office for the Americas (AMRO) Unit Chef, Comprehensive Family Immunization</p>
<p>Serhan, Fatima World Health Organization Immunization, Vaccines and Biologicals, IVB/EPI</p>
<p>Simon, Jonathon World Health Organization Research and Development, MCA/MRD</p>
<p>Vekemans, Johan World Health Organization Immunization, Vaccines and Biologicals, IVB/IVR</p>
<p>Velandia Gonzalez, Martha World Health Organization</p>
<p>Vicari, Andrea World Health Organization Immunization, Vaccines and Biologicals, IVB/IVR</p>
<p>Were, Wilson Milton World Health Organization Policy, Planning and Programmes, MCA/PPP</p>
<p>Wootton, Emily World Health Organization Immunization, Vaccines and Biologicals, IVB/EPI</p>
<p>Yakubu, Ahmadu World Health Organization Immunization, Vaccines and Biologicals, IVB/EPI</p>
<p>Zaffran, Michel World Health Organization Polio Eradication, POL</p>



Contents

- 561 Meeting of the Strategic Advisory Group of Experts on immunization, October 2016 – conclusions and recommendations
- 583 Monthly report on dracunculiasis cases, January–October 2016

Sommaire

- 561 Réunion du Groupe stratégique consultatif d'experts sur la vaccination, octobre 2016 – conclusions et recommandations
- 583 Rapport mensuel des cas de dracunculose, janvier–octobre 2016

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

The Strategic Advisory Group of Experts (SAGE) on immunization¹ met on 18–20 October 2016. This report summarizes the discussions, conclusions and recommendations.²

Report from the WHO Department of Immunization, Vaccines and Biologicals

The report addressed 4 main themes: the progress and failures observed; the current and recurrent challenges; the actions taken to accelerate progress; and the role of WHO.

The contribution of vaccination to the global reduction of mortality in children aged <5 years, and the broader impact of immunization in economic and productivity gains as well as community benefits were noted. SAGE emphasized the need for stronger communication on these health and non-health benefits of immunization.

The report noted that an additional 5.9 million children need to be vaccinated to achieve the goal of 90% 3rd dose diphtheria-tetanus-pertussis vaccine (DTP3) coverage by 2020. It called for accelerating the use of pneumococcal conjugate vaccine (PCV) and rotavirus vaccine as both have led to substantial reductions in childhood mortality.

The report cautioned that as immunization programmes are becoming more

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

Le Groupe stratégique consultatif d'experts (SAGE) sur la vaccination¹ s'est réuni du 18 au 20 octobre 2016. Le présent rapport résume les discussions, conclusions et recommandations auxquelles il est parvenu.²

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

Le rapport présenté était axé sur 4 thèmes principaux: les progrès et les échecs observés; les difficultés existantes et récurrentes; les mesures prises pour accélérer les progrès; et le rôle de l'OMS.

Le rapport a évoqué la contribution de la vaccination à la réduction mondiale de la mortalité des enfants de <5 ans, ainsi que ses retombées positives plus générales sur l'économie, la productivité et le bien-être des communautés. Le SAGE a souligné la nécessité d'intensifier les efforts de communication pour mieux faire connaître les avantages de la vaccination, tant dans le domaine de la santé que dans d'autres domaines.

Le rapport a indiqué que 5,9 millions d'enfants supplémentaires devront être vaccinés pour atteindre l'objectif d'une couverture de 90% par la 3^e dose de vaccin antidiphthérique-antitétanique-anticoquelucheux (DTC3) d'ici 2020. Il a appelé à une utilisation accélérée du vaccin antipneumococcique conjugué (VPC) et du vaccin antirotavirus, qui ont tous deux contribué à la baisse substantielle de la mortalité de l'enfant.

Le rapport a fait valoir que face à la complexité croissante des programmes de vaccination,

WORLD HEALTH
ORGANIZATION
Geneva

ORGANISATION MONDIALE
DE LA SANTÉ
Genève

Annual subscription / Abonnement annuel
Sw. fr. / Fr. s. 346.–

12.2016
ISSN 0049-8114
Printed in Switzerland

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

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

complex, recurrent challenges must be tackled boldly. Human and financial resources need to be strengthened. Staffing issues have restricted the expansion of vaccination coverage, particularly in the 10 countries with the most un- or under-vaccinated children. Capacity and support must be strengthened for frontline workers and mid-level managers. Repeated assessments of vaccine management using the WHO-UNICEF tool, Effective Vaccine Management (EVM), and planning corrective measures show substantive achievements in handling vaccine arrival, in improving cold chain storage capacity and understanding vaccine management policies and practices. SAGE expressed its appreciation of the new training and activities for mid-level staff and all efforts to address field challenges. On the ground, WHO is stepping up its technical assistance in priority countries, with funding support from GAVI. This will complement the work on strengthening routine immunization by staff funded through the Polio Eradication Programme.

In the African Region (AFR) the private-public partnership on meningitis A vaccination roll out has been successful and the vaccine has been introduced into national routine immunization programmes. AFR reported on the response to the large yellow fever (YF) outbreak occurring this year particularly in densely populated urban areas of Angola and the Democratic Republic of Congo (DRC). A fractional dose of YF vaccine was used to mitigate the impact of limited global vaccine supply. The worrying resurgence of polio in Nigeria was noted, in particular given the limited access to the parts of the country where the resurgence has occurred due to security concerns. Work is ongoing with countries, particularly those transitioning from donor funding, to establish resilient immunization systems, building on lessons learnt from the Ebola outbreak.

The Region of the Americas (AMR) celebrated the certification of elimination of endemic measles transmission in 2016. The Region focuses on providing immunization throughout the life course. The regional office is promoting the use of electronic vaccination records to improve data quality. Introductions of human papillomavirus (HPV) vaccine were negatively impacted by the cost of vaccine and anti-vaccination groups in some countries.

In the Eastern Mediterranean Region (EMR), despite strong efforts by the countries, DTP3 coverage has been declining due to acute and protracted emergencies, even in countries with historically high coverage. SAGE underlined the need for WHO to rapidly complete and roll out the guidance on vaccination in humanitarian emergencies. Middle income countries (MICs) in EMR are struggling with introducing (and sustaining) new vaccines in national programmes. Low income countries (LIC) benefiting from donor support show good progress.

certain défis récurrents devront être relevés de manière résolue. Un renforcement des ressources humaines et financières s'impose. Des problèmes de dotation en personnel ont ralenti l'expansion de la couverture vaccinale, en particulier dans les 10 pays comptant le plus grand nombre d'enfants non vaccinés ou insuffisamment vaccinés. Les capacités des agents de première ligne et des administrateurs de niveau intermédiaire doivent être renforcées, tout comme le soutien qui leur est apporté. Des évaluations répétées de la gestion des vaccins, effectuées au moyen de l'outil OMS-UNICEF de gestion efficace des vaccins (EVM), et la planification de mesures correctives ont révélé des progrès substantiels dans la réception des vaccins, les capacités de stockage de la chaîne du froid et la compréhension des politiques et des pratiques relatives à la gestion des vaccins. Le SAGE a exprimé sa satisfaction au vu des nouvelles activités et initiatives de formation destinées au personnel de niveau intermédiaire, ainsi que des efforts déployés pour surmonter les difficultés existantes sur le terrain. L'OMS s'emploie à intensifier l'assistance technique qu'elle offre sur le terrain aux pays prioritaires, avec l'appui financier de l'Alliance GAVI. Cette démarche s'inscrit en complément des activités de renforcement de la vaccination systématique engagées par le personnel mis à disposition par le programme d'éradication de la poliomyélite.

Dans la Région africaine, le lancement du partenariat public-privé sur la vaccination contre la méningite A a porté ses fruits et le vaccin a été introduit dans les programmes nationaux de vaccination systématique. La Région africaine a fait le point sur la riposte menée contre la flambée de fièvre jaune (FJ) de grande ampleur survenue cette année, en particulier dans certaines zones urbaines densément peuplées de l'Angola et de la République démocratique du Congo (RDC). Une dose fractionnée de vaccin antiamaril a été utilisée pour atténuer les effets de la pénurie mondiale de ce vaccin. Le rapport a rappelé l'inquiétude suscitée par la résurgence de la poliomyélite au Nigéria, la situation étant d'autant plus préoccupante que les parties du pays qui sont concernées sont difficilement accessibles en raison de problèmes de sécurité. Une collaboration se poursuit avec les pays, en particulier ceux qui sont en train de s'affranchir de l'aide financière des bailleurs de fonds, afin d'établir des systèmes de vaccination résilients en s'appuyant sur les enseignements tirés de la flambée d'Ebola.

Dans la Région des Amériques, la certification de l'élimination de la transmission endémique de la rougeole a été célébrée en 2016. La Région concentre ses efforts sur la prestation de services de vaccination à toutes les étapes de la vie. Le bureau régional s'emploie à promouvoir l'utilisation de dossiers électroniques de vaccination pour améliorer la qualité des données. L'introduction du vaccin contre le papillomavirus humain (PVH) s'est heurtée à des difficultés liées au coût du vaccin et à la présence de groupes anti-vaccination dans certains pays.

Dans la Région de la Méditerranée orientale, malgré les efforts considérables déployés par les pays, la couverture par le DTC3 est en régression suite à des situations d'urgence aiguës et prolongées, même dans les pays enregistrant ordinairement une couverture élevée. Le SAGE a souligné la nécessité d'une mise au point et d'une diffusion rapides des orientations de l'OMS sur la vaccination dans les situations d'urgence humanitaire. Les pays à revenu intermédiaire de la Région de la Méditerranée orientale peinent à introduire (et à maintenir) les nouveaux vaccins dans les programmes nationaux. Les pays à faible revenu bénéficiant d'un soutien financier de la part des bailleurs de fonds ont fait des progrès notables.

The European Region (EUR) is progressing steadily towards measles and rubella elimination despite not achieving the 2015 elimination goal. The importance of the regional vaccine action plan to steer collective actions towards 2020 and to advocate for elimination goals such as the recently endorsed viral hepatitis elimination strategy was stressed. EUR highlighted progress towards financial sustainability and vaccine price transparency, but needs further guidance for MICs graduating from donor support. Two major current concerns are lack of confidence in vaccination, and diphtheria antitoxin supply constraints which were highlighted by several fatal diphtheria cases during the last year.

The South-East Asia Region (SEAR) was congratulated for its elimination of maternal and neonatal tetanus (MNT). The successful tOPV to bOPV switch and the introduction of IPV in all countries were highlighted. A successful fractional dose approach was used during an IPV campaign in India. Sri Lanka also introduced fractional dose IPV in their routine programme. Three countries still need to introduce rubella vaccination. A hepatitis B control goal was set in June 2016. SEAR reported on the establishment of a voluntary regional network for national immunization technical advisory groups. Diphtheria outbreaks were reported from several countries in SEAR, occurring mainly in unvaccinated children as well as in older adults.

The Western Pacific Region (WPR) has made impressive achievements in hepatitis B reduction. WPR welcomed the political support for immunization programmes by the 67th Regional Committee meeting. Despite coverage disparities, there was good progress in achieving and maintaining high vaccination coverage. Although 8 countries were verified as having stopped transmission in 2016, there has been a resurgence of measles in other countries, mainly affecting adults and adolescents.

SAGE expressed its deep concern over the reported lack of diphtheria antitoxin and encouraged WHO to take on a strong leadership role in resolving this shortage globally.

SAGE further re-emphasized the need to integrate vaccination with other health programmes and the need to advance implementation research.

SAGE recommended engagement of local civil society organizations to improve vaccination coverage and the health system across all levels, including the subdistrict and community levels.

Report from GAVI, the Vaccine Alliance

The importance of SAGE recommendations in the work of the GAVI Alliance was highlighted, noting that SAGE's guidance is critical for understanding vaccine needs and immunization roll-out strategies.

La Région européenne avance à un rythme soutenu vers l'élimination de la rougeole et de la rubéole, bien que n'ayant pas atteint l'objectif d'élimination de 2015. L'importance que revêt le plan d'action régional pour les vaccins pour orienter les mesures collectives en vue de 2020 et promouvoir les objectifs d'élimination, comme ceux de la stratégie d'élimination de l'hépatite virale récemment adoptée, a été soulignée. La Région européenne a fait état des progrès accomplis en termes de viabilité financière et de transparence des prix des vaccins, mais aurait besoin d'orientations supplémentaires pour les pays à revenu intermédiaire en passe de s'affranchir de l'aide des donateurs. Deux phénomènes sont sources de préoccupations particulières pour la Région: le déficit de confiance à l'égard de la vaccination et les difficultés d'approvisionnement en antitoxine diphtérique, mises en exergue par plusieurs cas mortels de diphtérie survenus au cours de l'année.

Le SAGE a félicité la Région de l'Asie du Sud-Est d'être parvenue à éliminer le tétanos maternel et néonatal (TMN). La transition réussie du VPOT au VPOB et l'introduction du VPI dans tous les pays de la Région ont également été mises en exergue. Dans le cadre d'une campagne menée en Inde, l'administration de doses fractionnées de VPI s'est avérée concluante. Le Sri Lanka a également intégré une dose fractionnée de VPI dans son programme de vaccination systématique. Trois pays n'ont pas encore introduit la vaccination contre la rubéole. Un objectif de lutte contre l'hépatite B a été établi en juin 2016. La Région de l'Asie du Sud-Est a indiqué qu'un réseau régional destiné à réunir les groupes consultatifs techniques nationaux sur la vaccination avait été créé, reposant sur le principe de l'adhésion volontaire. Des flambées de diphtérie ont été signalées dans plusieurs pays de la Région, touchant principalement les enfants non vaccinés et les personnes âgées.

La Région du Pacifique occidental a obtenu des résultats impressionnants contre l'hépatite B. La Région s'est félicitée du soutien politique exprimé en faveur des programmes de vaccination lors de la 67e réunion du Comité régional. Malgré certaines disparités, des progrès importants ont été réalisés dans l'établissement et le maintien d'une forte couverture vaccinale. Bien que l'interruption de la transmission de la rougeole ait été vérifiée dans 8 pays de la Région en 2016, d'autres pays ont connu une resurgence de cette maladie, touchant essentiellement les adultes et les adolescents.

Le SAGE a fait part de ses vives inquiétudes face à la pénurie signalée d'antitoxine diphtérique et a encouragé l'OMS à jouer un rôle de premier plan pour remédier à ce problème à l'échelle mondiale.

Le SAGE a en outre réaffirmé la nécessité d'intégrer la vaccination à d'autres programmes de santé et de promouvoir la recherche opérationnelle.

Le SAGE a préconisé de mobiliser les organisations locales de la société civile en vue d'améliorer la couverture vaccinale et les systèmes de santé à tous les niveaux, y compris à l'échelle des sous-districts et des communautés.

Rapport de l'Alliance GAVI

L'Alliance GAVI a souligné l'importance qu'elle accorde aux recommandations du SAGE, indiquant que les orientations du SAGE lui sont d'un apport essentiel pour mieux cerner les besoins en vaccins et les stratégies de déploiement de la vaccination.

The goal to accelerate the global uptake of HPV vaccine to reduce cervical cancer mortality is of particular importance to GAVI from an equity perspective. More efforts are needed to accelerate the HPV vaccine uptake and the deliberations at SAGE will help GAVI focus its efforts and investments in this area.

To date, GAVI has invested over US\$ 300 million in YF control and is considering important additional investments towards improving the vaccine supply that would support the global strategy to eliminate YF epidemics.

In June 2016, the GAVI Board approved funding of up to US\$ 27.5 million to be matched by other donors for the RTS,S malaria vaccine pilot implementation projects recommended by SAGE. However, with UNITAID's commitment, there is still a gap of about US\$ 15 million. GAVI remains hopeful that other funders will come forward.

Other programme updates included: an overview of progress and shortfalls over the period 2011–2015; the ongoing engagement with India, Pakistan, DRC, Kenya, Madagascar and Nigeria to improve vaccination coverage and equity; addressing challenges in fragile countries and emergencies and the role of vaccine stockpiles in emergency vaccination.

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

GACVS met in June 2016³ and, inter alia, discussed the results from a cohort study of pentavalent vaccine in South India which provided support for the strong safety profile of the vaccine, and preliminary results of the first large scale use of dengue vaccine in the public sector in the Philippines. This latter campaign targeted 750 000 schoolchildren aged 9 and 10 years in 3 districts, of whom 67% of parents consented and 41% of children received the first dose. No safety concerns were identified.

GACVS undertook to monitor HPV vaccine safety, and has met on 6 occasions to discuss safety data, of which 3 took place in the early years following licensure. Thereafter, concerns related to anaphylaxis, syncope, an episode of mass psychogenic illness, autoimmune diseases including multiple sclerosis and Guillain-Barré syndrome (GBS) and venous thromboembolism were noted. Each of these signals was investigated with robust epidemiologic methods and each was confirmed as not related to vaccination. Notably, a large study in France using administrative data from over 2 million girls found no association between HPV vaccination and autoimmune disease, including multiple sclerosis. A small increased risk of GBS was noted, but this find-

L'accélération de l'adoption mondiale du vaccin contre le PVH pour réduire la mortalité due au cancer du col utérin est un objectif que l'Alliance juge particulièrement important du point de vue de l'équité. Estimant que des efforts plus soutenus doivent être consacrés à l'accélération de l'adoption de ce vaccin, l'Alliance entend s'appuyer sur les délibérations du SAGE pour orienter ses efforts et ses investissements dans ce domaine.

À ce jour, l'Alliance a investi plus de US\$ 300 millions dans la lutte contre la fièvre jaune et envisage de consentir d'importants investissements supplémentaires pour le renforcement de l'approvisionnement en vaccins afin d'appuyer la stratégie mondiale d'élimination de l'épidémie de fièvre jaune.

En juin 2016, le Conseil d'administration de l'Alliance a approuvé un financement à hauteur de US\$ 27,5 millions, devant être assorti de fonds jumelés par d'autres donateurs, pour les projets pilotes de mise en œuvre de la vaccination antipaludique par le RTS,S recommandés par le SAGE. Cependant, en comptant l'engagement pris par UNITAID, il subsiste un déficit de financement d'environ US\$ 15 millions. L'Alliance continue d'espérer que d'autres bailleurs de fonds se manifesteront.

L'Alliance a en outre fait le point sur les aspects programmatiques suivants: progrès et insuffisances dans la période 2011-2015; collaboration en cours avec l'Inde, le Kenya, Madagascar, le Nigéria, le Pakistan et la RDC pour améliorer la couverture vaccinale et l'équité; défis inhérents aux pays fragiles et aux situations d'urgence et rôle des stocks de vaccins pour la vaccination d'urgence.

Rapport du Comité consultatif mondial pour la sécurité des vaccins (GACVS)

Le GACVS s'est réuni en juin 2016.³ Ses discussions ont porté, entre autres, sur les résultats d'une étude de cohorte du vaccin pentavalent réalisée en Inde du Sud, qui ont témoigné d'un très bon profil d'innocuité du vaccin, ainsi que sur les résultats préliminaires de la première utilisation à grande échelle du vaccin contre la dengue dans le secteur public aux Philippines. La campagne aux Philippines ciblait 750 000 enfants scolarisés de 9 et 10 ans dans 3 districts. Un consentement parental a été obtenu pour 67% de ces enfants, et 41% ont reçu la première dose. Aucun problème de sécurité vaccinale n'a été identifié.

Dans le cadre de sa mission de surveillance de l'innocuité du vaccin anti-PVH, le GACVS s'est réuni à 6 reprises pour étudier les données de sécurité correspondantes. Trois de ces réunions ont eu lieu dans les premières années qui ont suivi l'homologation du vaccin. Par la suite, des inquiétudes ont été émises concernant le risque de réaction anaphylactique, de syncope, d'épisode de phénomène psychogénique de masse, de maladies auto-immunes, dont la sclérose en plaques et le syndrome de Guillain-Barré (SGB), et de thromboembolie veineuse. Chacun de ces signaux a été analysé à l'aide de méthodes épidémiologiques rigoureuses et il a été confirmé qu'aucun n'était lié à la vaccination. Il est à noter qu'une vaste étude menée en France à l'aide de données administratives portant sur plus de 2 millions de jeunes filles n'a révélé aucune association entre

³ See No. 28/29, 2016, pp. 341–348.

³ Voir N° 28/29, 2016, pp. 341-348.

ing contrasted with those of other large studies which did not find a similar association.

Unfortunately, in spite of evidence of safety, communities continue to have concerns. In Japan, claims of chronic pain syndrome, and in Denmark, reports of postural orthostatic tachycardia syndrome (POTS), resembling chronic fatigue syndrome, surfaced and had a substantial negative impact on the HPV vaccination programmes. Review of these perceived associations has not corroborated them.

Both GACVS and SAGE are concerned about the harm arising from public loss of confidence in HPV vaccines, but also noted some successes with high vaccination coverage in several countries, with scientific reports of reduction in cervical intraepithelial neoplasia in vaccinated women. Improving communication on demonstrated disease impact and evidence of vaccine safety, and formulation of effective messaging, are critical for maintaining vaccine confidence.

Report from the Product Development for Vaccines Advisory Committee (PDVAC)

In June 2016, PDVAC reviewed progress concerning previously prioritized pathogens, and the status of vaccine development against 7 new pathogens. Several parallel activities are underway to facilitate evidence-based decision making on respiratory syncytial virus (RSV) interventions, including pilot RSV surveillance in 16 countries and the development of an international standard reagent for RSV neutralization assays. SAGE also recommended establishment of a prequalification pathway for monoclonal antibodies.

WHO held its first consultation on Group B streptococcal vaccines in April 2016, and with vaccine candidates from 3 manufacturers in development, efforts are underway to develop WHO preferred product characteristics (PPCs).

Activities to support development of enterotoxigenic *E. coli* and *Shigella* vaccines have been initiated, with a focus on developing PPCs, including consensus building on clinical endpoints and study design for phase III efficacy studies, and understanding data requirements for regulatory and policy perspectives for both single and combination vaccines.

In line with PDVAC recommendations, WHO will facilitate consensus building with respect to the development of PPCs for tuberculosis vaccines for prevention of pulmonary disease in adolescents and adults, which would also reduce transmission. Consideration will also be needed on how best to assess the role of new recombinant BCG approaches compared to the existing BCG vaccine.

la vaccination anti-PVH et les maladies auto-immunes, dont la sclérose en plaques. Un risque légèrement accru de SGB a été observé, mais ce résultat s'inscrit en faux par rapport aux conclusions d'autres grandes études n'ayant pas trouvé d'association de ce type.

Malheureusement, malgré les preuves d'innocuité du vaccin, les communautés continuent de se montrer inquiètes. Les allégations de syndrome de douleur chronique au Japon et la notification de cas de syndrome de tachycardie orthostatique posturale (semblable au syndrome de fatigue chronique) au Danemark ont eu un impact négatif considérable sur les programmes de vaccination contre le PVH. Ces associations présumées n'ont pas été corroborées par les enquêtes menées.

Le GACVS et le SAGE sont tous 2 préoccupés par le préjudice occasionné par la perte de confiance du public envers les vaccins anti-VPH, mais se félicitent de certains succès rencontrés dans plusieurs pays où la couverture de la vaccination est élevée et où des rapports scientifiques font état d'une réduction du nombre de cas de néoplasie cervicale intraépithéliale chez les femmes vaccinées. Pour préserver la confiance à l'égard du vaccin, il est indispensable d'améliorer la communication sur l'impact démontré de la maladie et les preuves d'innocuité du vaccin et de formuler des messages plus efficaces.

Rapport du Comité consultatif sur le développement de produits pour les vaccins (PDVAC)

En juin 2016, le PDVAC a examiné les progrès réalisés contre les pathogènes qui avaient préalablement été désignés comme prioritaires et a fait le point des efforts de mise au point de vaccins contre 7 nouveaux pathogènes. Plusieurs activités ont été engagées en parallèle pour faciliter une prise de décision fondée sur des données probantes concernant les interventions contre le virus respiratoire syncytial (VRS), notamment une étude pilote de surveillance du VRS dans 16 pays et l'élaboration d'un réactif de référence international pour les épreuves de neutralisation du VRS. Le SAGE a également recommandé qu'une voie de préqualification soit instaurée pour les anticorps monoclonaux.

L'OMS a tenu sa première consultation sur les vaccins contre les streptocoques du groupe B en avril 2016 et, tandis que 3 fabricants s'emploient à mettre au point des vaccins candidats, des efforts sont en cours pour élaborer les caractéristiques de produit préférées par l'OMS.

Des activités ont été engagées pour favoriser la mise au point de vaccins contre *Escherichia coli* entérotogène et *Shigella*, axées principalement sur l'élaboration des caractéristiques de produit préférées, notamment la recherche d'un consensus sur les critères cliniques et la structure des études d'efficacité de phase III, et la compréhension des exigences réglementaires et politiques en matière de données, tant pour les vaccins simples que combinés.

Conformément aux recommandations du PDVAC, l'OMS facilitera la recherche d'un consensus sur les caractéristiques de produit préférées pour les vaccins antituberculeux destinés à prévenir les pneumopathies chez l'adulte et l'adolescent, ce qui réduirait également la transmission de la maladie. Il conviendra aussi de réfléchir au meilleur moyen d'évaluer le rôle des nouveaux vaccins BCG recombinants par rapport au vaccin BCG existant.

In the last year Zika vaccine target product profiles (TPPs), and multivalent filovirus TPPs have been developed with oversight by PDVAC and within the R&D blueprint framework.

In 2017, PDVAC will undertake activities to support development of vaccines against Group A streptococcus and sexually transmitted infections.

Report from the Implementation Research Advisory Committee (IVIR-AC)

In June 2016⁴, IVIR-AC discussed missed opportunities for vaccination, non-specific effects of vaccines, research to conduct impact evaluation of vaccines in use, rotavirus mortality, a guide for disease and economic impact model comparisons, HPV modelling in low and middle income countries, influenza-specific economic guidelines, cholera disease burden and research on electronic registries for immunization programmes.

The report stressed that for the last 20 years there has been a steep rise in the use of mathematical models for disease and economic impact projections of new and underutilized vaccines, for which assumptions and subjective choices on model design are necessary. IVIR-AC began providing guidance on model comparisons to better understand model designs and their uncertainties in order to better inform decision-making. IVIR-AC calls for open access and transparent databases to facilitate comparison of models.

Protocols for clinical trials to study the non-specific effects of vaccines have been drafted and will be reviewed. Proposals will be presented to SAGE next year.

Report from international immunization partners

This session was a continuation of a series of presentations initiated in 2015 on the immunization-related activities of international partner organizations; MSF and UNICEF were invited to present at the first session. The presentations focus on the partners' contributions to implementation of the WHO Global Vaccine Action Plan (GVAP).

During the current meeting, the World Bank Group (WBG) described how it supports immunization programmes across low and middle income countries, highlighted the constraints these programmes are facing, and outlined their role in ensuring financial and institutional sustainability of immunization programmes. The role of WBG in supporting sustainable funding for health system strengthening, and

Durant l'année écoulée, des profils de produits cibles ont été élaborés pour les vaccins contre le Zika et les vaccins multivalents contre les filovirus, sous la supervision du PDVAC et dans le cadre du Schéma directeur en matière de recherche et développement.

En 2017, le PDVAC entreprendra des activités destinées à soutenir la mise au point de vaccins contre les streptocoques du groupe A et les infections sexuellement transmissibles.

Rapport du Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC)

Lors de la réunion de l'IVIR-AC en juin 2016,⁴ différents thèmes ont été abordés: les occasions manquées de vaccination, les effets non spécifiques des vaccins, la recherche pour évaluer l'impact des vaccins utilisés, la mortalité due aux rotavirus, un guide pour la comparaison des modèles sur l'incidence économique et l'impact sur les maladies, les modèles relatifs au PVH dans les pays à revenu faible ou intermédiaire, des orientations économiques sur la grippe, la charge de morbidité du choléra et la recherche sur l'utilisation de registres électroniques dans les programmes de vaccination.

Le rapport a indiqué que les 20 dernières années ont été marquées par une utilisation très importante de la modélisation mathématique pour établir des projections de l'incidence économique et de l'impact sur les maladies des vaccins nouveaux et sous-utilisés, imposant d'adopter des hypothèses et de faire des choix subjectifs quant à la structure des modèles. L'IVIR-AC a commencé à formuler des orientations sur la comparaison des modèles pour permettre une meilleure compréhension de leur structure et de leurs incertitudes, en appui au processus décisionnel. L'IVIR-AC appelle au libre accès et à la transparence des bases de données afin de faciliter la comparaison des modèles.

Des protocoles d'essais cliniques visant à étudier les effets non spécifiques des vaccins ont été élaborés et seront soumis à examen. Des propositions dans ce sens seront présentées au SAGE l'an prochain.

Rapport des partenaires internationaux dans le domaine de la vaccination

Cette session s'inscrivait dans la continuité d'une série de présentations, lancée en 2015, sur les activités relatives à la vaccination des organisations internationales partenaires. Médecins sans frontières et l'UNICEF avaient été invités à intervenir lors de la première session. Ces présentations portent essentiellement sur les contributions des partenaires à la mise en œuvre du Plan d'action mondial pour les vaccins (GVAP) de l'OMS.

Durant la présente réunion, le Groupe de la Banque mondiale a décrit le soutien qu'il apporte aux programmes de vaccination dans les pays à revenu faible ou intermédiaire, les contraintes auxquelles ces programmes sont confrontés et sa contribution à la pérennité financière et institutionnelle des programmes de vaccination. Il a mis l'accent sur le rôle qu'il joue pour favoriser un financement durable des activités de renforcement des systèmes de santé et appuyer les capacités de vaccination

⁴ See No. 33, 2016, pp. 389–396.

⁴ Voir N° 33, 2016, 91, pp. 389-396.

service and programmatic capacity for immunization delivery through careful analytical work to inform policy dialogue, were emphasized. Effective coverage of immunization as an essential element of universal health coverage was stressed.

The Bill and Melinda Gates Foundation (BMGF) presented its activities and outlined its 4 strategic areas in support of the GVAP – vaccine delivery, discovery and vaccine development, disease-specific areas of work, and advocacy and policy. The BMGF stressed that reducing inequities in health starts with achievement of high vaccination coverage and that documenting subnational data is key to improving suboptimal coverage. In a specific example, lack of consistency in mapping of geographic borders led to uncertainties about responsibilities and was therefore a barrier for programme implementation.

SAGE expressed appreciation for the immunization-related work of both organizations and encourages countries to take advantage of immunization support through the WBG. SAGE was pleased by the catalytic work of BMGF and the innovations it fosters, and encouraged countries and partners to benefit fully from the knowledge generated and the implementation of strategies with demonstrated impact. SAGE stressed the need for access to the findings from this work so that it could be fully leveraged.

Polio eradication

SAGE acknowledged the progress made towards eliminating wild poliovirus (WPV) transmission. In the past 12 months 49 WPV cases were reported (as of 12 October 2016) in Afghanistan, Nigeria and Pakistan. In Afghanistan and Pakistan, the overall situation has significantly improved with increased access and quality of supplementary immunization activities (SIA), progress in highest risk areas of traditional reservoirs (i.e. Peshawar, FATA, Quetta, and Balochistan), and strong coordination between these countries. In Nigeria, 4 WPV cases and 1 isolate in a community contact were detected in July and August 2016, the first reported from Africa in more than 2 years; the strain appears to have circulated for >4 years prior to its detection.

Following the withdrawal of oral polio vaccine type 2 (OPV2) in April 2016, 19 type 2 vaccine-derived polioviruses (VDPV2) have been detected. In Nigeria circulating vaccine-derived polioviruses (cVDPV2) were detected in an environmental sample in March and in a healthy child in August 2016, reflecting presence of persistent cVDPVs, last detected in northern Nigeria in November 2014. No other cVDPV2 has been detected since the OPV2 withdrawal. Environmental surveillance indicated that Sabin type 2 virus quickly disappeared from environmental samples after May 2016.

Despite the overall progress, SAGE expressed concern over the undetected circulation of persistent cVDPV2 and WPV1 in Nigeria and reiterated the importance of monitoring surveillance quality especially in Tier 1 and

des services et des programmes grâce à un travail analytique rigoureux visant à éclairer le dialogue politique. L'importance d'une couverture vaccinale efficace, composante essentielle de la couverture sanitaire universelle, a été soulignée.

La Fondation Bill & Melinda Gates a présenté ses activités et a décrit les 4 domaines stratégiques de son action en faveur du GVAP: distribution des vaccins; découverte et mise au point des vaccins; domaines d'activité spécifiques à certaines maladies; et plaidoyer et action politique. La Fondation Bill & Melinda Gates a fait valoir que la réduction des inégalités sanitaires passe avant tout par la mise en place d'une forte couverture vaccinale et que la collecte de données infranationales est essentielle pour améliorer la couverture lorsque cette dernière est sous-optimale. Elle a évoqué un exemple précis, dans lequel le manque de cohérence dans la cartographie des frontières géographiques a engendré des incertitudes quant à la répartition des responsabilités, entravant la mise en œuvre du programme.

Le SAGE a salué le travail réalisé par ces 2 organisations dans le domaine de la vaccination et a encouragé les pays à tirer parti de l'appui à la vaccination proposé par le Groupe de la Banque mondiale. Le SAGE a exprimé sa satisfaction pour l'action catalytique de la Fondation Bill & Melinda Gates et les innovations qu'elle favorise et a encouragé les pays et les partenaires à tirer pleinement parti des connaissances générées et de la mise en œuvre de stratégies ayant un impact avéré. Le SAGE a souligné la nécessité d'un accès aisé aux résultats de ces travaux pour en favoriser l'exploitation.

Éradication de la poliomyélite

Le SAGE a salué les progrès accomplis en vue d'éliminer la transmission des poliovirus sauvage (PVS). Au cours des 12 derniers mois, 49 cas de PVS ont été notifiés (au 12 octobre 2016) en Afghanistan, au Nigéria et au Pakistan. En Afghanistan et au Pakistan, la situation globale s'est nettement améliorée, avec un accès accru et une meilleure qualité des activités de vaccination supplémentaire (AVS), des progrès enregistrés dans les zones les plus à risque des réservoirs traditionnels (Peshawar, zones tribales sous administration fédérale, Quetta et Baloutchistan) et une coordination renforcée entre ces pays. Au Nigéria, 4 cas de PVS et 1 isolat chez un contact communautaire ont été identifiés en juillet et août 2016, constituant la première détection en Afrique depuis plus de 2 ans; il semble que la souche ait circulé pendant >4 ans avant d'être détectée.

Suite au retrait du vaccin antipoliomyélitique oral de type 2 (VPO2) en avril 2016, 19 poliovirus dérivés d'une souche vaccinale de type 2 (PVDV2) ont été détectés. Au Nigéria, des poliovirus circulants dérivés d'une souche vaccinale (PVDVc2) ont été identifiés dans un échantillon prélevé dans l'environnement en mars, ainsi que chez un enfant sain en août 2016, témoignant de la présence de PVDVc persistants, dont la dernière détection, dans le nord du Nigéria, datait de novembre 2014. Aucun autre PVDVc2 n'a été détecté depuis le retrait du VPO2. La surveillance environnementale indique que la souche Sabin de type 2 a rapidement disparu des échantillons environnementaux après mai 2016.

Malgré l'amélioration globale de la situation, le SAGE s'est dit préoccupé par la circulation non détectée de PVDVc2 persistants et de PVS1 au Nigéria et a réitéré l'importance d'un bon suivi de la qualité de la surveillance, en particulier dans les

2 countries and other access-limited areas. SAGE noted the proposed changes in the type 2 outbreak response protocol with more limited use of mOPV2 (i.e. from 4–5 to 2–3 rounds depending on the coverage achieved and transmission risks) due to further evidence of the high efficacy of mOPV2. SAGE recognizes that IPV may also be an effective tool in a type 2 response, but its use will need to be carefully targeted due to global supply limitation.

In addition, SAGE agreed with the Polio Working Group's assessment that immunodeficiency-related vaccine-derived polioviruses (iVDPV) could constitute a risk of seeding communities and triggering outbreaks. SAGE endorsed the proposed approach to expand AFP surveillance to detect more iVDPVs by screening suspected primary immunodeficiency patients for poliovirus excretion.

SAGE reviewed the report on the globally synchronized withdrawal of OPV2 and commended the successful completion of the switch in all 155 countries, and IPV introduction in 105 of 126 OPV-only countries.

However, SAGE noted that the IPV supply situation is further deteriorating; 50 countries are experiencing delays in supply or stock-outs, a situation which is likely to persist until 2018. Any further decline in IPV supply would affect the supply to Tier 1 and 2 countries.

Given this situation and the high efficacy of 2-dose fractional intradermal IPV, SAGE strongly recommended that: (i) countries should start preparing for a fractional intradermal dose IPV 2-dose schedule, e.g. at 6 and 14 weeks, in lieu of a single intramuscular full dose at 14 weeks (as implemented in India and Sri Lanka); (ii) the programme should explore the possible use of devices facilitating intradermal administration (e.g. jet injectors, intradermal adapters); and (iii) whenever deemed necessary, outbreak response campaigns with IPV should only be conducted with an intradermal fractional dose. It urged WHO to facilitate discussions and decision-making by National Immunization Technical Advisory Groups (NITAGs) to introduce this option by providing necessary technical information. While the intradermal administration of IPV is off-label, public health authorities such as SAGE and NITAGs not uncommonly make recommendations that differ from the labelled use (e.g. hepatitis A, human papillomavirus, influenza, pneumococcal, and yellow fever vaccines), especially in emergency situations.

SAGE recommended that when sufficient supplies of IPV become available countries with delayed IPV introduction or stock-outs should prepare for catch-up vaccination of children who could not receive IPV in the routine schedule.

pays de niveaux 1 et 2 et d'autres zones d'accès limité. Le SAGE a pris note des changements proposés pour le protocole de riposte aux flambées de type 2, prévoyant un usage plus limité du VPOM2 (avec 2-3 tournées au lieu de 4-5 tournées, selon la couverture obtenue et les risques de transmission) au vu des données supplémentaires confirmant la grande efficacité du VPOM2. Le SAGE reconnaît que le VPI pourrait également constituer un outil efficace dans la riposte aux flambées de type 2, mais son utilisation devra être ciblée avec soin en raison de sa disponibilité mondiale limitée.

En outre, le SAGE souscrit à l'évaluation du Groupe de travail sur la poliomyélite, selon laquelle les poliovirus dérivés d'une souche vaccinale associés à une immunodéficience (PVDVi) peuvent présenter un risque d'implantation dans les communautés et de déclenchement de flambées. Le SAGE a approuvé l'approche proposée pour étendre la surveillance de la PFA et détecter un plus grand nombre de PVDVi par dépistage de l'excrétion de poliovirus parmi les patients chez lesquels un déficit immunitaire primaire est soupçonné.

Le SAGE a examiné le rapport sur le retrait synchronisé du VPO2 à l'échelle mondiale et s'est félicité de l'exécution réussie de la transition dans l'ensemble des 155 pays et de l'introduction du VPI dans 105 des 126 pays où seul le VPO était utilisé.

Toutefois, le SAGE a indiqué que la situation relative à l'approvisionnement en VPI a continué de se détériorer; 50 pays sont confrontés à des retards d'approvisionnement ou des ruptures de stocks, une situation qui persistera probablement jusqu'en 2018. Tout déclin supplémentaire des stocks de VPI risquerait de compromettre l'approvisionnement des pays de niveaux 1 et 2.

Compte tenu de cette situation et de la grande efficacité du VPI intradermique en 2 doses fractionnées, le SAGE a vivement recommandé que: i) les pays commencent à se préparer à l'adoption d'un schéma d'administration de 2 doses fractionnées de VPI par voie intradermique, par exemple à 6 et 14 semaines, au lieu d'une dose unique complète par voie intramusculaire à 14 semaines (comme l'ont fait l'Inde et le Sri Lanka); ii) les programmes explorent les possibilités d'utilisation de dispositifs facilitant l'administration intradermique (injecteurs sous pression, adaptateurs intradermiques); et iii) lorsque cela est jugé nécessaire, les campagnes de riposte aux flambées par le VPI reposent exclusivement sur l'administration d'une dose fractionnée intradermique. Le SAGE a vivement encouragé l'OMS à faciliter les débats et la prise de décision par les groupes consultatifs techniques nationaux sur la vaccination (NITAG) quant à l'adoption de cette option en fournissant les informations techniques nécessaires. Bien que l'administration intradermique du VPI constitue une utilisation hors indication de ce vaccin, il n'est pas inhabituel que le SAGE et les NITAG émettent des recommandations qui diffèrent des indications homologuées (par exemple pour les vaccins contre l'hépatite A, le papillomavirus humain, la grippe, les infections à pneumocoques et la fièvre jaune), en particulier en situation d'urgence.

Le SAGE a recommandé aux pays ayant subi un retard d'introduction du VPI ou des ruptures de stock de se préparer à assurer une vaccination de rattrapage, une fois que des stocks suffisants de VPI seront disponibles, auprès des enfants n'ayant pas reçu le VPI dans le cadre de la vaccination systématique.

SAGE acknowledged the progress made in implementing containment of poliovirus, including official reports on WPV2/VDPV2 inventories completed in 176/205 countries and territories, and 21 workshops.

SAGE welcomed and endorsed the development of the Containment Certification Scheme (CCS) which supplements and supersedes Annex 4 of the Global Action Plan (GAPIII) to minimize poliovirus facility-associated risk after type-specific eradication of WPVs and sequential cessation of OPV use, and urged national authorities to start preparing for containment certification based on the CCS.

SAGE also requested WHO to complete the guidance on identification of potentially infectious materials (including stool and respiratory specimens) into 3 groups based on likelihood of being contaminated with VDPV2 or WPV2.

Lastly, SAGE reviewed the Working Group's discussion on future polio immunization policy. SAGE agreed that countries may not require additional bOPV campaigns prior to OPV cessation, except for areas with high risk of infection and low routine immunization coverage such as areas with under-vaccinated and/or inaccessible subpopulations.

SAGE agreed that the post-OPV immunization schedule should aim to achieve at least 90% seroconversion, which will be achieved with at least 2 doses of IPV (either full or fractional) and that countries will need to continue routine immunization with IPV after the certification of polio eradication for an extended period (e.g. 5, 10 or more years). The Working Group was requested to make more detailed recommendations (e.g. minimum duration of use of IPV, options for IPV schedule) for the post-OPV immunization schedule to SAGE in April 2017.

Measles and rubella elimination

SAGE reviewed the findings and recommendations from the Midterm Review (MTR) of the Global Measles and Rubella Strategic Plan, 2012–2020 and commended the review team on its work. SAGE endorsed the key findings and recommendations, in particular, that the basic strategies in the strategic plan are sound, and that failure to reach global targets is mainly due to lack of country ownership and global political will, as reflected in insufficient resources.

Although all 6 WHO Regions have measles elimination goals, SAGE considered it premature to set a timeframe for global eradication at this point. A determination should be made, not later than 2020, on whether a formal global goal for measles eradication should be set with timeframes for achievement. Meantime, all regions should work towards achieving the regional elimination goals.

Le SAGE s'est félicité des progrès réalisés en matière de confinement des poliovirus, saluant notamment les rapports officiels indiquant que 176/205 pays et territoires ont achevé l'inventaire des établissements détenant des PVS2/PVDV2 et que 21 ateliers ont été organisés.

Le SAGE a favorablement accueilli et approuvé l'élaboration du dispositif de certification du confinement (CCS), qui complète et remplace l'annexe 4 du Plan d'action mondial (GAPIII), visant à réduire au minimum le risque associé aux poliovirus détenus dans les établissements après l'éradication par type des PVS et l'abandon séquentiel du VPO, et a vivement encouragé les autorités nationales à se préparer à la certification du confinement selon le CCS.

Le SAGE a également demandé à l'OMS de compléter ses orientations sur l'identification des matériels potentiellement infectieux (y compris les échantillons de selles et prélèvements respiratoires), à catégoriser en 3 groupes selon la probabilité de contamination par les PVDV2 ou PVS2.

Enfin, le SAGE a fait le point des délibérations du Groupe de travail sur la poliomyélite concernant les futures politiques de vaccination antipoliomyélique. Le SAGE a convenu que les pays n'auront peut-être pas besoin de mener des campagnes supplémentaires d'administration du VPO avant l'arrêt du VPO, à l'exception des zones présentant un risque élevé d'infection et une faible couverture de la vaccination systématique, comme celles où vivent des sous-populations insuffisamment vaccinées et/ou inaccessibles.

Le SAGE a convenu qu'après l'arrêt du VPO, le calendrier vaccinal devra viser une séroconversion d'au moins 90%, obtenue par l'administration d'au moins 2 doses de VPI (complètes ou fractionnées), et a indiqué que les pays devront poursuivre la vaccination systématique par le VPI pendant une période prolongée (5 ans, 10 ans ou plus) après la certification de l'éradication de la poliomyélite. Il a été demandé au Groupe de travail sur la poliomyélite de formuler des recommandations plus détaillées concernant le calendrier de vaccination après l'arrêt du VPO (par exemple durée minimale d'utilisation du VPI, options relatives au schéma d'administration du VPI), à soumettre au SAGE en avril 2017.

Élimination de la rougeole et de la rubéole

Le SAGE a examiné les conclusions et recommandations issues de l'évaluation à mi-parcours du Plan stratégique mondial 2012-2020 de lutte contre la rougeole et la rubéole et a félicité l'équipe d'évaluation pour son travail. Le SAGE a souscrit aux principales conclusions et recommandations, convenant en particulier que le plan repose sur des stratégies fondamentales solides et que la non-réalisation des cibles mondiales s'explique principalement par une appropriation insuffisante du programme par les pays et par l'absence de volonté politique à l'échelle mondiale, comme en témoigne l'insuffisance des ressources consacrées à cet effort.

Bien que les 6 Régions de l'OMS aient toutes établi des objectifs d'élimination de la rougeole, le SAGE estime qu'il serait prématuré, à ce stade, de fixer une échéance pour l'éradication mondiale de la maladie. Il conviendra de déterminer, au plus tard d'ici 2020, si un objectif mondial formel d'éradication de la rougeole devrait être établi, assorti d'échéances à respecter. Entre-temps, il importe que toutes les Régions s'emploient à atteindre les objectifs régionaux d'élimination.

SAGE welcomed the additional GAVI investment in measles and rubella as a major step towards achieving measles and rubella goals. However, this investment alone is insufficient to achieve these goals, as many countries are not GAVI-eligible or are graduating from GAVI-eligibility. Key global strategies such as surveillance and research are also under-resourced.

SAGE supported the key recommendations from the MTR for strengthening disease surveillance as disease incidence is the most important indicator of programmatic success. SAGE stressed the importance of: high routine vaccination coverage with 2 doses of MCV in order to achieve and sustain high population immunity at national and subnational levels; having updated strategies for outbreak preparedness and response; more effective communication and engagement with the public; increasing research and development particularly for implementation science; building on the polio transition; placing greater attention on governance; and intensification of resource mobilization and advocacy. SAGE also stressed the need for stronger political will and resources, the importance of measles and rubella vaccination programmes in building national routine immunization programmes, and the preference for use of rubella⁵ in combination with measles rather than stand-alone measles vaccine. SAGE supported the call for a budgeted implementation plan within 12 months.

SAGE highlighted the risk of resurgence of measles and other vaccine-preventable diseases among countries with significant polio resources that contribute to supporting the overall immunization and surveillance programmes. Similarly, GAVI-graduating countries will face difficulties in sustaining the current levels of control unless early and specific measures are taken to address these impending funding gaps. SAGE recommended that countries should take advantage of GAVI Health Systems and Immunization Strengthening (HSIS) funding, particularly to strengthen surveillance infrastructure.

SAGE stressed the critical role of high quality measles and rubella case-based surveillance and recommended that, as countries approach elimination, they should intensify surveillance and move towards weekly reporting to the Regions.

Given the changing epidemiology in some countries, SAGE expressed the need to address the immunity gaps

Le SAGE a accueilli avec satisfaction l'investissement supplémentaire consenti par l'Alliance GAVI dans la lutte contre la rougeole et la rubéole, estimant qu'il s'agit d'un pas important vers la réalisation des objectifs relatifs à ces maladies. Toutefois, cet investissement ne suffira pas à lui seul à atteindre les objectifs fixés, étant donné que de nombreux pays ne remplissent pas les conditions nécessaires pour bénéficier de l'aide de l'Alliance ou sont en passe de s'affranchir de cette aide. Certaines approches stratégiques mondiales clés, comme celles qui ont trait à la surveillance et à la recherche, souffrent également d'un manque de ressources.

Le SAGE a appuyé les principales recommandations de l'évaluation à mi-parcours relatives au renforcement de la surveillance des maladies, l'incidence étant l'indicateur le plus important de la réussite programmatique. Le SAGE a souligné l'importance des éléments suivants: une couverture élevée de la vaccination systématique par 2 doses de MCV pour obtenir et maintenir une forte immunité de la population aux niveaux national et infranational; la présence de stratégies actualisées de préparation et de riposte aux flambées; une communication plus efficace et des échanges accrus avec le public; un renforcement des activités de recherche et développement, en particulier en science de la mise en œuvre; la mise à profit de la transition opérée pour la poliomyélite; une attention accrue portée aux questions de gouvernance; l'intensification des efforts de plaidoyer et de mobilisation des ressources. Le SAGE a également mis l'accent sur la nécessité d'une volonté politique plus forte et de ressources accrues, le rôle important joué par les programmes de vaccination contre la rougeole et la rubéole dans le renforcement des programmes nationaux de vaccination systématique, et la préférence accordée à l'utilisation d'un vaccin combiné contre la rubéole⁵ et la rougeole, plutôt qu'un vaccin uniquement antirougeoleux. Le SAGE a soutenu l'appel à la préparation d'un plan budgétisé de mise en œuvre dans un délai de 12 mois.

Le SAGE a attiré l'attention sur le risque de résurgence de la rougeole et d'autres maladies à prévention vaccinale dans les pays où d'importantes ressources consacrées à la lutte contre la poliomyélite sont mises à contribution pour appuyer les programmes généraux de vaccination et de surveillance. De même, les pays s'affranchissant de l'aide de l'Alliance GAVI auront des difficultés à maintenir leur niveau actuel de maîtrise des maladies à moins que des mesures précoces et spécifiques soient prises pour combler ces déficits imminents de financement. Le SAGE a préconisé que les pays tirent profit des possibilités de financement au titre du programme de renforcement des systèmes de santé et de la vaccination de l'Alliance GAVI, en particulier pour renforcer l'infrastructure de surveillance.

Le SAGE a souligné qu'il est crucial d'assurer une surveillance de la rougeole et de la rubéole qui soit de haute qualité et basée sur l'identification des cas, et a recommandé aux pays, alors qu'ils s'approchent de l'objectif d'élimination, d'intensifier la surveillance et de commencer à transmettre des rapports hebdomadaires aux Régions.

Compte tenu de l'évolution de l'épidémiologie de la maladie dans certains pays, le SAGE a fait valoir qu'il sera nécessaire de

⁵ In countries meeting the WHO criteria for the introduction of rubella containing vaccines into national immunization programmes as outlined in the rubella vaccine position paper. See No. 29, 2011, pp. 301–316.

⁵ Dans les pays répondant aux critères de l'OMS relatifs à l'introduction des vaccins à valence rubéole dans les programmes nationaux de vaccination, tels que décrits dans la note de synthèse concernant les vaccins antirougeoleux. Voir N° 29, 2011, pp. 301-316.

among adolescents and adults by removing regulatory and policy barriers and promoting effective strategies for vaccinating them. SAGE supported the development by WHO of a standardized method to categorize countries based on their level of disease control and likelihood of achieving and sustaining measles and rubella elimination, and tailoring immunization and surveillance strategies to the country categorization.

SAGE acknowledged the importance of operational and technological research to address the barriers to achieving GVAP measles and rubella goals. In particular, SAGE recommended that the most expeditious clinical development and regulatory pathway to licensure of measles containing vaccines (MCV) micro-array patch (MAP) be determined, and that barriers to the development, licensure, and use of MAPs for measles and rubella vaccine delivery be identified and addressed urgently.

SAGE was requested to consider the removal of the criterion for the introduction of routine measles second dose as stated in the 2009 measles vaccine position paper.⁶ SAGE recommended that a routine second dose of MCV (MCV2) should be added to national immunization schedules in all countries regardless of level of MCV1 coverage.

The removal of the introduction criterion would help improve equity of access to vaccine in countries with weaker immunization systems as well as allowing these countries time to improve their coverage with the second routine dose. And adding a routine MCV2 can serve to establish a well-child visit in the second year of life, provide a timely opportunity for catch-up in children who missed MCV1 or any other vaccine, potentially reduce MCV wastage, and, based on current evidence, does not negatively impact MCV1 coverage. SAGE emphasized that children older than 24 months should also be checked for missed vaccinations and be vaccinated as needed.

SAGE stressed that the accumulation of susceptible persons at both the national and subnational level should continue to be monitored to identify and address immunity gaps. SAGE requested that the Measles and Rubella Working Group refine the recommendations as to when follow-up SIAs should be conducted.

Maternal and neonatal tetanus elimination (MNTE) and broader tetanus prevention

SAGE reviewed the report from the Working Group on MNTE and broader tetanus prevention and considered the draft recommendations.

SAGE noted that while there was progress with MNTE, there are still 18 countries which have still have not achieved MNTE elimination, resulting in the goal of

combler les lacunes en matière d'immunité des adultes et des adolescents en éliminant les barrières réglementaires et politiques et en encourageant la mise en œuvre de stratégies efficaces de vaccination de ces groupes. Le SAGE a soutenu l'élaboration par l'OMS d'une méthode normalisée de catégorisation des pays selon leur niveau de maîtrise de la maladie et la probabilité qu'ils parviennent à une élimination durable de la rougeole et de la rubéole, avec une adaptation des stratégies de vaccination et de surveillance en fonction de la catégorie de chaque pays.

Le SAGE a reconnu l'importance que revêt la recherche opérationnelle et technologique pour lever les obstacles à la réalisation des objectifs du GVAP relatifs à la rougeole et à la rubéole. En particulier, le SAGE a recommandé d'identifier les voies de développement clinique et d'autorisation réglementaire les plus rapides pour parvenir à l'homologation de timbres à micro-aiguilles pour l'administration des vaccins à valence rougeole (MCV), indiquant qu'il était urgent d'identifier et d'éliminer les obstacles à la mise au point, à l'homologation et à l'utilisation des timbres à micro-aiguilles pour l'administration des vaccins antirougeoleux et antirubéoleux.

Il a été demandé au SAGE d'envisager le retrait du critère relatif à l'introduction de la seconde dose systématique de vaccin antirougeoleux tel que mentionné dans la note de synthèse de 2009.⁶ Le SAGE a préconisé l'ajout d'une seconde dose systématique de MCV (MCV2) dans les calendriers vaccinaux nationaux de tous les pays, quelle que soit la couverture par le MCV1.

Le retrait du critère d'introduction permettrait de renforcer l'égalité d'accès au vaccin dans les pays où les systèmes de vaccination sont moins robustes et donnerait à ces pays plus de temps pour améliorer leur couverture par la seconde dose systématique. En outre, l'ajout d'une dose MCV2 systématique permettrait d'instaurer une consultation de contrôle durant la deuxième année de vie, fournirait une occasion opportune de rattrapage chez les enfants qui auraient manqué la dose MCV1 ou toute autre vaccination, permettrait éventuellement de réduire le gaspillage de MCV et, selon les données actuelles, n'aurait pas d'impact négatif sur la couverture par le MCV1. Le SAGE a souligné qu'il est également important de vérifier qu'aucune vaccination n'a été manquée chez les enfants de plus de 24 mois, et de vacciner ces enfants si nécessaire.

Le SAGE a ajouté que l'accumulation de personnes sensibles à la maladie, tant au niveau national qu'infranational, doit continuer de faire l'objet d'un suivi en vue d'identifier et de combler les lacunes immunitaires. Le SAGE a demandé au Groupe de travail sur la rougeole et la rubéole d'affiner les recommandations relatives au calendrier des AVS de suivi.

Élimination du tétanos maternel et néonatal (TMN) et prévention générale du tétanos

Le SAGE a examiné le rapport et le projet de recommandations du Groupe de travail sur l'élimination du TMN et la prévention générale du tétanos.

Le SAGE a constaté qu'en dépit des progrès accomplis, 18 pays ne sont toujours pas parvenus à éliminer le TMN, l'objectif d'élimination mondiale (qui était fixé à l'horizon 2015) n'ayant

⁶ See No. 35, 2009, pp. 349–360.

⁶ Voir N° 35, 2009, pp. 349-360.

global elimination (set for 2015) being missed once again. The failure to achieve this goal is a reminder of persisting health inequities and the inability of some countries to provide basic health services to the most marginalized and vulnerable populations.

SAGE noted that the earlier recommendations to shift from the use of tetanus toxoid (TT) to combinations containing diphtheria toxoid (DT or Td vaccines) have not yet been implemented in many countries despite the negligible price differential between TT and DT/Td vaccines, and recommended that WHO and UNICEF take steps to accelerate the shift.

SAGE also took note of the emerging immunity gaps among adolescents (females and males) and adult males in countries with no booster dose routine programme and where TT-containing vaccines are only offered during pregnancy or in SIAs targeting females of reproductive age. These immunity gaps came to the attention of the global community through cases of tetanus in those undergoing voluntary medical male circumcision (VMMC) as part of the WHO recommended HIV control programme.

Based on the review of evidence, SAGE made the following recommendations:

General recommendations for MNTE

- Countries, international organizations and development agencies should prioritize the implementation of all strategies to achieve and sustain MNTE, including routine immunization of pregnant women, routine antenatal care, clean delivery and cord care and improved surveillance and reporting of tetanus cases.
- There should be greater involvement and oversight by the WHO Regional Offices, regional and national TAGs in monitoring progress and ensuring that the global goal of MNTE is achieved. The regional and national TAGs should play an important role in advocating for the actions required from countries and partners.

Specific recommendations for countries yet to achieve elimination

- Countries yet to achieve MNTE should establish/update and implement their operational plans to achieve the required action within the timelines stated in the report from the Working Group on MNTE and broader tetanus prevention. Achievement of MNTE by 2020 is feasible with timely availability of financial resources and compact single-dose pre-filled auto-disable injection devices (CPAD) to reach the most marginalized population groups.
- UNICEF, United Nations Population Fund (UNFPA) and WHO should support countries in securing the necessary resources to implement their national

de ce fait de nouveau pas pu être atteint. La non-réalisation de cet objectif témoigne de la persistance des inégalités sanitaires et de l'incapacité de certains pays à fournir des services de santé de base aux populations les plus vulnérables et marginalisées.

Le SAGE a constaté que dans de nombreux pays, les recommandations précédentes portant sur l'abandon de l'anatoxine tétanique (AT) au profit de vaccins combinés contenant l'anatoxine diphtérique (vaccins DT ou Td) n'ont pas encore été pleinement mises en œuvre malgré l'écart de prix négligeable entre les vaccins AT et DT/Td. Il a recommandé à l'OMS et à l'UNICEF de prendre des mesures pour accélérer cette transition.

Le SAGE a également pris note des lacunes immunitaires émergentes chez les adolescents (filles et garçons) et chez les hommes adultes dans les pays dépourvus de programmes d'administration systématique d'une dose de rappel et où les vaccins contenant l'AT sont uniquement offerts pendant la grossesse ou dans le cadre d'AVS ciblant les femmes en âge de procréer. Ces lacunes immunitaires ont été portées à l'attention de la communauté mondiale lorsque des cas de tétanos ont été identifiés parmi des sujets se soumettant à une circoncision masculine médicalisée volontaire dans le cadre du programme de lutte anti-VIH recommandé par l'OMS.

Sur la base de l'examen des données existantes, le SAGE a formulé les recommandations suivantes:

Recommandations générales pour l'élimination du TMN

- Les pays, les organisations internationales et les organismes d'aide au développement devront accorder la priorité à la mise en œuvre de toutes les stratégies permettant de parvenir à l'élimination durable du TMN, y compris la vaccination systématique des femmes enceintes, la prestation de soins prénatals de routine, la pratique d'accouchements et de soins du cordon ombilical dans de bonnes conditions d'hygiène et l'amélioration de la surveillance et de la notification des cas de tétanos.
- Une participation et une surveillance accrues sont nécessaires de la part des bureaux régionaux de l'OMS et des groupes consultatifs techniques régionaux et nationaux pour suivre les progrès et veiller à la réalisation de l'objectif mondial d'élimination du TMN. Les groupes consultatifs techniques régionaux et nationaux sont appelés à jouer un rôle important de plaidoyer pour inciter les pays et les partenaires à agir.

Recommandations spécifiques pour les pays n'ayant pas encore atteint l'objectif d'élimination

- Les pays n'ayant pas encore atteint l'objectif d'élimination du TMN devront établir/actualiser et appliquer leurs plans opérationnels pour parvenir aux actions requises dans les délais fixés dans le rapport du Groupe de travail sur l'élimination du TMN et la prévention générale du tétanos. L'élimination du TMN à l'horizon 2020 est un objectif réalisable sous réserve de la disponibilité de ressources financières suffisantes et de dispositifs d'injection compacts préremplis autobloquants à dose unique pour atteindre les groupes de population les plus marginalisés.
- L'UNICEF, le Fonds des Nations Unies pour la population (UNFPA) et l'OMS devront aider les pays à obtenir les ressources nécessaires pour mettre en œuvre leurs plans

elimination plans, including procurement of Td vaccine and operational costs for SIAs.

- UNICEF, UNFPA and WHO should make all efforts to secure timely supply of the available WHO prequalified TT⁷ vaccine in CPAD 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 predictable and timely funding support for the remaining 18 countries, if the 2020 elimination timeline is to be met.

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 commitment to maintaining elimination of MNT, in order to guard against complacency once a country has been declared to have achieved elimination.
- All immunization programmes should review and adjust routine immunization schedules to ensure tetanus protection over the life course (3 priming doses in infancy and 3 booster doses in childhood/adolescence) and documentation of doses received should be ensured. All countries should scale up and sustain the coverage with clean delivery and improve clean cord care practices.
- Annual monitoring of maternal and child health (MCH), surveillance and EPI district performance through joint desk review of core⁸ and surrogate⁹ 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.
- Td vaccination campaigns should be conducted in the districts identified as being at high risk in order to fill immunity gaps.
- Steps should be taken to improve the quality of monitoring, case investigation, and reporting of tetanus cases as part of a strengthened surveillance and reporting system; the surveillance data should be used for decision-making and surveillance should be the primary mechanism for monitoring sustained MNTE.

⁷ There is unfortunately no prequalified Td vaccine in CPAD.

⁸ TT2+ coverage, skilled birth attendance coverage, neonatal tetanus rate per 1000 live births.

⁹ Antenatal care coverage, DTP1 and DTP3 immunization coverage, and percentage of population urban vs rural.

nationaux d'élimination, notamment pour l'achat des vaccins Td et les coûts opérationnels liés aux AVS.

- L'UNICEF, l'UNFPA et l'OMS devront déployer tous les efforts nécessaires pour garantir un approvisionnement en temps utile du vaccin AT⁷ en dispositif compact prérempli autobloquant préqualifié par l'OMS pour faciliter la vaccination des populations inaccessibles par les agents communautaires. Si les stocks de vaccin AT sous cette forme sont moins importants qu'escompté, un plan clair d'établissement des priorités et d'allocation des doses disponibles devra être établi.
- L'UNICEF, l'UNFPA et l'OMS devront de toute urgence élaborer un dossier d'investissement relatif au TMN et formuler une stratégie de mobilisation des ressources pour garantir un appui financier rapide et prévisible aux 18 pays restants, condition nécessaire à la réalisation de l'objectif d'élimination à l'horizon 2020.

Recommandations spécifiques pour assurer la pérennité de l'élimination du TMN dans tous les pays prioritaires ayant atteint l'objectif d'élimination depuis 1999

- L'UNICEF, l'UNFPA et l'OMS devront collaborer avec les pays en vue de mobiliser et de maintenir l'engagement politique à l'égard des efforts de pérennisation de l'élimination du TMN afin d'éviter une baisse de la vigilance dans les pays où l'élimination a été déclarée.
- Il convient que tous les programmes de vaccination examinent et adaptent leurs calendriers de vaccination systématique pour garantir une protection à vie contre le tétanos (3 doses de primovaccination chez le nourrisson, suivies de 3 doses de rappel durant l'enfance/l'adolescence) et la documentation des doses reçues. Tous les pays doivent s'employer à accroître durablement la proportion d'accouchements réalisés dans de bonnes conditions d'hygiène et améliorer les pratiques de soins du cordon ombilical.
- Le suivi annuel de la santé de la mère et de l'enfant, la surveillance et l'évaluation de la performance du Programme élargi de vaccination au niveau des districts au moyen d'un examen conjoint sur dossier des indicateurs de risque de base⁸ et de substitution⁹ du TMN constituent un moyen utile et bien adapté d'identifier les districts à haut risque et de surveiller le risque potentiel de TMN. Les résultats devraient servir de base à l'élaboration de mesures correctives en matière de vaccination et de services de santé de la mère et de l'enfant.
- Des campagnes de vaccination par le Td devront être menées dans les districts identifiés comme présentant un risque élevé afin de combler les lacunes immunitaires.
- Des mesures devront être prises pour améliorer la qualité du suivi, l'investigation des cas et la notification des cas de tétanos dans le cadre d'un système renforcé de surveillance et de notification; il conviendra de s'appuyer sur les données de surveillance dans le processus décisionnel et de considérer la surveillance comme le principal outil de suivi de l'élimination durable du TMN.

⁷ Il n'existe malheureusement pas de vaccin Td préqualifié sous forme de dispositif d'injection compact prérempli autobloquant.

⁸ Couverture AT2+, proportion d'accouchements en présence de personnel qualifié, taux de tétanos néonatal pour 1000 naissances vivantes.

⁹ Couverture des soins prénatals, couverture de la vaccination par le DTC1 et DTC3, et pourcentage de la population urbaine par rapport à la population rurale.

Recommendations for achieving broader tetanus prevention

- The 3 booster dose schedule intended to achieve protection throughout adulthood (reproductive age for women) and beyond, thereby likely providing lifelong protection, should preferably be given during the second year of life, at age 4–7 years, and at age 9–15 years. WHO should re-emphasize the previous recommendations¹⁰ on the number of doses needed in women of reproductive age if SIAs or routine immunization of pregnant women are needed and clarify that pregnant women are protected when they have had 5–6 documented doses (by card, immunization registry and/or history) by the time of reproductive age in order to avoid unnecessary repeat vaccinations for protection during pregnancies. The number of doses ensuring protection depends on when these doses were given and the interval between doses.
- 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 throughout 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 aged 4 years and older.
- In view of serosurvey data showing declining seroprotection with increasing age in the absence of booster doses, as well as recent tetanus cases in the VMMC programme, updated WHO recommendations should reinforce the need for booster doses for both males and females throughout the life course, opportunistic catch-up immunization, individual and community education on clean wound care and following standard surgical protocols as per the WHO infection prevention guidelines.
- Where feasible, the use of serosurveys to validate assessment of risk identified 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 provide guidance on: sampling methods; sample collection and testing; and analysis, interpretation and use of serosurvey data for monitoring.
- WHO should consider establishing reference laboratories and reference serum panels to support standardization and quality assurance of the laboratory methods used in serosurveys.

¹⁰ See No. 20, 2006, pp. 197–208.

Recommandations pour parvenir à la prévention générale du tétanos

- Les 3 doses de rappel destinées à conférer une protection à l'âge adulte (à l'âge de procréer pour les femmes) et au-delà, permettant ainsi probablement une immunisation à vie, devront de préférence être administrées durant la deuxième année de vie, puis à l'âge de 4-7 ans et à l'âge de 9-15 ans. Il convient que l'OMS réitère ses recommandations antérieures¹⁰ sur le nombre de doses requises chez les femmes en âge de procréer si des AVS ou une vaccination systématique des femmes enceintes sont nécessaires, en précisant en outre que les femmes enceintes sont protégées dès lors qu'elles ont reçues 5-6 doses documentées (par carnet de vaccination, registre de vaccination et/ou antécédents) avant d'arriver à l'âge de procréer, cette précision étant nécessaire pour éviter que des vaccinations répétées inutiles ne leur soient administrées durant la grossesse. Le nombre de doses nécessaires pour obtenir la protection requise dépend de la chronologie des doses administrées et de l'intervalle écoulé entre chaque dose.
- Il est recommandé à l'OMS de réitérer sa recommandation relative à l'utilisation de vaccins combinés contenant l'anatoxine tétanique et l'anatoxine diphtérique pour stimuler et maintenir l'immunité antidiphtérique tout au long de la vie, aussi bien chez les hommes que chez les femmes, de suivre l'adoption de cette recommandation, et de préciser que l'association de l'antigène tétanique avec l'antigène diphtérique faiblement dosé (Td) est l'option programmatique à privilégier pour les enfants âgés de 4 ans ou plus.
- Au vu des données issues des enquêtes sérologiques, indiquant que la séroprotection diminue avec l'âge en l'absence de doses de rappel, et compte tenu des cas de tétanos récemment identifiés dans le cadre du programme de circoncision masculine médicalisée volontaire, les recommandations de l'OMS devraient être actualisées pour souligner la nécessité d'administrer des doses de rappel aussi bien aux hommes qu'aux femmes tout au cours de la vie, d'assurer une vaccination opportuniste de rattrapage, de fournir une éducation individuelle et communautaire sur le soin hygiénique des plaies et de veiller à l'application de protocoles chirurgicaux standard conformes aux lignes directrices de l'OMS sur la prévention des infections.
- Dans la mesure du possible, on devra envisager de réaliser des enquêtes sérologiques permettant de valider l'évaluation des risques identifiés à partir d'autres sources de données afin de guider les stratégies de vaccination, en particulier dans les districts à haut risque. Une attention particulière doit être portée aux stratégies d'échantillonnage et aux méthodes de laboratoire pour garantir la validité et l'interprétabilité des résultats. L'OMS devra fournir des orientations sur: les méthodes d'échantillonnage; le prélèvement des échantillons et les tests réalisés; et l'analyse, l'interprétation et l'utilisation des données issues des enquêtes sérologiques aux fins de la surveillance.
- L'OMS devra envisager d'établir des laboratoires de référence et des panels de sérums de référence pour favoriser la standardisation et l'assurance de la qualité des méthodes de laboratoire utilisées lors des enquêtes sérologiques.

¹⁰ Voir N° 20, 2006, pp. 197-208.

Global Vaccine Action Plan: 2016 mid-term review of progress and recommendations

At the mid-term of the Decade of Vaccines, the GVAP secretariat prepared a detailed report¹¹ on progress against each of the GVAP indicators¹² and included a section on “Sustainable financing and supply for immunization” to detail the activities initiated in response to the WHA resolution on access to affordable vaccines¹³ and progress reports from the regions¹⁴ and from some priority countries.¹⁵

The SAGE Working Group for the Decade of Vaccines (DoV)¹⁶ reviewed this GVAP secretariat report and prepared a SAGE GVAP assessment report that was then discussed, amended and then endorsed¹⁷ by SAGE.

At the midpoint of the GVAP, SAGE remains very concerned that progress toward the goals to eradicate polio, eliminate measles and rubella, and eliminate maternal and neonatal tetanus is too slow. 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. Twenty-six of these countries reported no change and 25 reported a net decrease in coverage since 2010.

However, SAGE sees many reasons to be hopeful that immunization will provide the cornerstone for health programmes around the world for decades to come. Sixteen countries, including some of the countries with the highest numbers of un- or under-vaccinated children, have made measurable progress since 2010 and are to be commended for reaching more children. Research and development efforts are accelerating the discovery and testing of an expanded portfolio of vaccine candidates and platform delivery technologies. Once these have been tested, licensed and deployed at scale, they will have a powerful impact on health and well-being around the world.

SAGE recommends that countries demonstrate stronger leadership and governance of national immunization systems.

- a) Ministers at all levels should be strong immunization advocates within their countries and regions. These high-level officials should be able to convey the high return on investment, the urgency and

Plan d'action mondial pour les vaccins: évaluation à mi-parcours de 2016 et recommandations

À l'issue de l'évaluation à mi-parcours de la Décennie de la vaccination, le secrétariat du GVAP a préparé un rapport détaillé¹¹ des progrès réalisés pour chacun des indicateurs¹² du GVAP, avec une section sur «le financement et l'approvisionnement durables pour la vaccination» décrivant les activités entreprises pour donner suite à la résolution de l'Assemblée mondiale de la Santé sur l'accès aux vaccins à un prix abordable¹³ et aux rapports de situation transmis par les Régions¹⁴ et par certains pays prioritaires.¹⁵

Le Groupe de travail du SAGE sur la Décennie de la vaccination¹⁶ a examiné le rapport du secrétariat du GVAP et préparé un rapport SAGE d'évaluation du GVAP qui a par la suite été étudié, amendé et approuvé¹⁷ par le SAGE.

À mi-parcours du GVAP, le SAGE demeure vivement préoccupé par la lenteur des progrès réalisés vers l'éradication de la poliomyélite, l'élimination de la rougeole et de la rubéole et l'élimination du tétanos maternel et néonatal. La couverture vaccinale moyenne n'a progressé que de 1% à l'échelle mondiale depuis 2010. En 2015, 68 pays ne sont pas parvenus à atteindre l'objectif d'une couverture nationale d'au moins 90% par la troisième dose de vaccin antidiphtérique-antitétanique-anticoquelucheux. Parmi ces pays, 26 ont signalé une stagnation de leur couverture nationale et 25 avaient enregistré un déclin net de leur couverture depuis 2010.

Cependant, le SAGE a de nombreuses raisons de croire que la vaccination sera la clé de voûte des programmes de santé dans le monde entier au cours des décennies à venir. Seize pays, parmi lesquels figurent des pays comptant les taux les plus élevés d'enfants non vaccinés ou insuffisamment vaccinés, ont réalisé des progrès tangibles depuis 2010 et méritent d'être félicités pour les efforts qu'ils ont déployés pour atteindre un plus grand nombre d'enfants. Les activités de recherche et développement ont permis d'accélérer le processus de découverte et de mise à l'essai d'un portefeuille élargi de vaccins candidats et de plateformes technologiques de vaccination. Ces produits, une fois testés, homologués et déployés à plus grande échelle, auront un impact puissant sur la santé et le bien-être dans le monde entier.

Le SAGE recommande aux pays de faire preuve d'un leadership et d'une gouvernance plus solides dans le cadre des systèmes de vaccination nationaux.

- a) Les ministres doivent à tous les niveaux être de fervents défenseurs de la vaccination dans leurs pays et régions. Ces responsables de haut niveau devraient faire connaître l'excellent retour sur investissement, l'importance et l'urgence

¹¹ See http://www.who.int/entity/immunization/global_vaccine_action_plan/gvap_secretariat_report_2016.pdf?ua=1

¹² See http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/

¹³ See http://apps.who.int/gb/ebwha/pdf_files/WHA68-REC1/A68_R1_REC1-en.pdf, page 38

¹⁴ See http://www.who.int/entity/immunization/global_vaccine_action_plan/2_Regional_reports_annex_GVAP_secretariat_report_2016.pdf?ua=1

¹⁵ See http://www.who.int/entity/immunization/global_vaccine_action_plan/3_Country_reports_annex_GVAP_secretariat_report_2016.pdf?ua=1

¹⁶ See http://www.who.int/immunization/sage/sage_wg_decade_vaccines/en/

¹⁷ See http://www.who.int/entity/immunization/global_vaccine_action_plan/SAGE_GVAP_Assessment_Report_2016_EN.pdf

¹¹ Voir http://www.who.int/entity/immunization/global_vaccine_action_plan/gvap_secretariat_report_2016.pdf?ua=1

¹² Voir http://www.who.int/immunization/global_vaccine_action_plan/DoV_GVAP_2012_2020/fr/

¹³ Voir http://apps.who.int/gb/ebwha/pdf_files/WHA68-REC1/A68_2015_REC1-fr.pdf, page 39

¹⁴ Voir http://www.who.int/entity/immunization/global_vaccine_action_plan/2_Regional_reports_annex_GVAP_secretariat_report_2016.pdf?ua=1

¹⁵ Voir http://www.who.int/entity/immunization/global_vaccine_action_plan/3_Country_reports_annex_GVAP_secretariat_report_2016.pdf?ua=1

¹⁶ Voir http://www.who.int/immunization/sage/sage_wg_decade_vaccines/en/

¹⁷ Voir http://www.who.int/entity/immunization/global_vaccine_action_plan/SAGE_GVAP_Assessment_Report_2016_FR.pdf

value of investing more in and sustaining immunization programmes as an integral part of government-supported Universal Health Coverage packages.

- b) Governments are encouraged to enact laws that guarantee access to immunization, establish NITAGs or equivalent 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 the private sector).
- c) National leaders must take courageous decisions to upgrade systems, protocols, and policies that are necessary to achieve and sustain high immunization coverage. Such upgrades might require redesigning supply chains, information systems and procurement policies, and reassessing roles and responsibilities in case the government decides to implement the decentralization of the health system.
- d) National immunization programme managers should report each year to their NITAGs or equivalent groups 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.

SAGE recommends that countries 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 later adulthood.
- b) The 34 countries with DTP3 national coverage levels below 80% should accelerate the implementation of proven interventions to strengthen immunization systems as part of integrated health services. Countries, with advice from the NITAGs or equivalent, should identify and implement priority interventions, including human resource development, increase of domestic funding for immunization and improved quality and use of data.

SAGE recommends that countries secure necessary investments to sustain immunization during polio and GAVI transitions.

- a) All countries should mitigate any threat to sustaining effective immunization programmes when polio funding decreases. Countries with large numbers of staff and resources provided through the Global Polio Eradication Initiative are requested to describe, in their polio transition plan, how they

d'investir davantage dans les programmes de vaccination et d'en assurer la pérennité, en tant que partie intégrante de la couverture sanitaire universelle financée par l'État.

- b) Les gouvernements sont encouragés à promulguer des lois qui garantissent l'accès à la vaccination, à établir des NITAG ou des groupes équivalents, à veiller chaque année à l'allocation de budgets suffisants aux fins de la vaccination et à créer des mécanismes pour suivre et gérer de manière efficace les fonds à tous les niveaux (y compris ceux venant du secteur privé).
- c) Les responsables au niveau national doivent prendre des décisions courageuses en vue d'améliorer les systèmes, les protocoles et les politiques nécessaires pour atteindre et maintenir une forte couverture vaccinale. Il est possible que ces améliorations supposent une réorganisation des chaînes d'approvisionnement, des systèmes d'information et des politiques d'achat, ainsi qu'une réévaluation des rôles et des responsabilités dans le cas où les pouvoirs publics décideraient de mettre en œuvre une décentralisation du système de santé.
- d) Chaque année, les administrateurs des programmes de vaccination nationaux doivent faire rapport aux NITAG ou aux groupes équivalents pour les informer des progrès accomplis, des enseignements tirés et des défis restant à relever dans la mise en œuvre des plans de vaccination nationaux et montrer comment ces plans sont alignés sur les objectifs des plans d'action régional et mondial pour les vaccins.

Le SAGE recommande aux pays d'accorder la priorité au renforcement des systèmes de vaccination.

- a) Il conviendrait que les pays étendent les services de vaccination, au-delà des nourrissons et des enfants, à tous les groupes d'âge, et déterminent les moyens les plus efficaces et économiques d'atteindre d'autres tranches d'âge dans le cadre d'une prestation intégrée des services de santé. De nouvelles plateformes sont requises de toute urgence pour atteindre les populations au cours de la deuxième année de vie, ainsi que durant l'enfance, l'adolescence, la grossesse et l'âge adulte plus avancé.
- b) Les 34 pays dont les niveaux de couverture nationale par le DTC3 sont inférieurs à 80% doivent accélérer la mise en œuvre d'interventions qui ont fait leurs preuves afin de renforcer les systèmes de vaccination dans le cadre de services de santé intégrés. Les pays, sur l'avis des NITAG ou des groupes équivalents, doivent identifier et mettre en œuvre des interventions prioritaires, notamment le développement des ressources humaines, l'augmentation du financement national pour la vaccination, ainsi que l'amélioration de la qualité et de l'utilisation des données.

Le SAGE recommande aux pays d'obtenir les investissements nécessaires pour maintenir la vaccination pendant les phases de transition relatives à la poliomyélite et au financement de l'Alliance GAVI

- a) Tous les pays doivent atténuer les risques éventuels que représente la diminution des financements consacrés à la poliomyélite pour le maintien de programmes de vaccination efficaces. Il est demandé aux pays où le personnel employé et les ressources mobilisées par l'Initiative mondiale pour l'éradication de la poliomyélite sont importants de

propose to maintain and fund critical immunization, laboratory and surveillance activities that are currently supported with polio funding and staff.

- b) In all countries transitioning from GAVI support, national and global immunization partners 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.

SAGE recommends that countries 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; establishing a clear process for investigating and confirming cases of vaccine preventable diseases; and responding to and preventing outbreaks.
- b) Decision-makers at all levels of the immunization programme are requested to use up-to-date data (i.e. disease surveillance, coverage, and programme delivery data) to guide programmatic and strategic decisions that reduce disease and protect at-risk populations.

SAGE also made several important recommendations to the immunization partners and the DoV secretariat, which are detailed in its SAGE GVAP Assessment report 2016.¹⁷

SAGE reaffirmed that immunization is one of the world's most effective and cost-effective tools against both the threat of emerging diseases and antimicrobial resistance and has a powerful impact on social and economic development.

Hepatitis B vaccination

Safe and effective vaccines against hepatitis B have been available since 1982. As of 2015, 185 (95%) countries worldwide had introduced hepatitis B vaccination in their infant schedules with 97 (49%) countries providing the recommended birth dose. WHO has estimated that 84% of all infants worldwide received at least 3 doses of hepatitis B containing vaccine in 2015 and 39% of newborns received the birth dose. Vaccinating against hepatitis B has been associated with substantial reductions in the incidence of acute and chronic hepatitis B infections and mortality from hepatocellular carcinoma.

SAGE was presented with systematic reviews related to immunization schedules in infants; immunization dose and schedules for particular groups such as HIV

décrire, dans leurs plans de transition, comment ils se proposent de maintenir et de financer les activités critiques de vaccination, de laboratoire et de surveillance qui dépendent actuellement des ressources financières ou humaines dévolues à la lutte contre la poliomyélite.

- b) Dans tous les pays qui sont en passe de s'affranchir de l'aide de l'Alliance GAVI, les partenaires nationaux et mondiaux de la vaccination doivent plaider avec fermeté et opiniâtreté en faveur d'une augmentation du financement intérieur pour pérenniser les acquis de la vaccination.
- c) Les donateurs doivent aussi regarder au-delà de leurs investissements dans l'Alliance GAVI pour s'assurer que les pays s'affranchissant de l'aide de l'Alliance, les pays autonomes et les pays confrontés à une forte baisse du financement destiné à la lutte contre la poliomyélite disposent des capacités, des outils et des ressources nécessaires pour maintenir la vaccination à long terme.

Le SAGE recommande aux pays d'améliorer leurs capacités de surveillance, ainsi que la qualité et l'utilisation des données.

- a) Il convient que tous les pays renforcent et pérennisent leurs capacités de surveillance en investissant dans les systèmes de détection et de notification des cas, les systèmes d'analyse systématique et de notification des données et le renforcement des capacités de laboratoire; en établissant un processus clair d'investigation et de confirmation des cas de maladies à prévention vaccinale; et en déployant des efforts de riposte et de prévention des flambées.
- b) Il est demandé aux décideurs à tous les niveaux des programmes de vaccination d'utiliser des données actualisées (sur la surveillance, la couverture et l'exécution des programmes) pour orienter les décisions programmatiques et stratégiques en vue de réduire la charge de morbidité et de protéger les populations à risque.

Le SAGE a également formulé plusieurs recommandations importantes à l'intention des partenaires de la vaccination et du secrétariat de la Décennie de la vaccination, présentées en détail dans le Rapport SAGE d'évaluation du GVAP de 2016.¹⁷

Le SAGE a réaffirmé que la vaccination est l'un des outils les plus efficaces et les plus économiques dont dispose le monde pour lutter contre la menace que représentent les maladies émergentes et la résistance aux antimicrobiens. Il a rappelé que les retombées positives de la vaccination sur le développement social et économique sont considérables.

Vaccination contre l'hépatite B

Il existe des vaccins sûrs et efficaces contre l'hépatite B depuis 1982. En 2015, le vaccin contre l'hépatite B figurait dans le calendrier de vaccination des nourrissons de 185 (95%) pays du monde, dont 97 (49%) assuraient comme recommandé l'administration d'une dose à la naissance. L'OMS estime qu'en 2015, 84% des nourrissons dans le monde ont reçu au moins 3 doses de vaccin contre l'hépatite B et 39% des nouveau-nés ont bénéficié de la dose à la naissance. Il a été observé que la vaccination contre l'hépatite B est corrélée à une baisse substantielle de l'incidence des infections aiguës et chroniques par le virus de l'hépatite B, ainsi que de la mortalité liée au carcinome hépatocellulaire.

Le SAGE a pris connaissance des revues systématiques qui lui ont été présentées, portant sur: les calendriers de vaccination des nourrissons; les doses et calendriers de vaccina-

infected, low birth weight infants and individuals with occupational increased risk of exposure to hepatitis B including health-care workers; and whether there is a need for a booster dose. Evidence identified through systematic review on long-term impact of vaccination on hepatitis B epidemiology had been used for modelling the prevalence of hepatitis B virus infections and their complications including liver cirrhosis and hepatocellular carcinoma.

SAGE concluded that infant hepatitis B vaccination achieves substantial protection against chronic HBsAg carriage, which will ultimately result in significant reductions of cirrhosis and hepatocellular carcinoma.

SAGE reemphasized the importance of the birth dose and urged all countries to introduce the universal birth dose without further delay.

All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours. If this is not feasible, the birth dose can still be effective in preventing perinatal transmission if given within 7 days, particularly within 3 days, although somewhat less than if given within 24 hours, but with declining effectiveness with each passing day. Even after 7 days, a late birth dose can be effective in preventing horizontal transmission and therefore remains beneficial. Thus, SAGE recommends that all infants receive the birth dose during the first contact with health facilities at any time up to the time of the first primary dose. The birth dose given after 24 hours should be reported as a late birth dose vaccination.

The birth dose should be followed by 2 or 3 doses to complete the primary series. Both of the following options are 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.

No changes were proposed by SAGE in the current recommendations related to booster doses, the interval between doses or in the recommendations for special populations – including for HIV-infected individuals, low birth weight infants and individuals with increased occupational risk for hepatitis B infection such as health-care workers.

A systematic review and a survey had been conducted with the aim of identifying barriers to providing the birth dose.

tion applicables à des groupes particuliers, comme les personnes infectées par le VIH, les nourrissons en insuffisance pondérale à la naissance et les personnes présentant un risque accru d'exposition à l'hépatite B sur leur lieu de travail, notamment les agents de santé; et la nécessité ou non d'une dose de rappel. Les données issues d'une revue systématique des effets à long terme de la vaccination sur l'épidémiologie de l'hépatite B ont été utilisées pour modéliser la prévalence des infections par le virus de l'hépatite B, ainsi que des complications associées, dont la cirrhose du foie et le carcinome hépatocellulaire.

Le SAGE a conclu que la vaccination des nourrissons contre l'hépatite B confère une protection substantielle contre le portage chronique de l'HBsAg, qui mènera à terme à un recul important de la cirrhose et du carcinome hépatocellulaire.

Le SAGE a réitéré l'importance que revêt la vaccination à la naissance et a vivement encouragé tous les pays à introduire sans plus attendre une dose universelle à la naissance dans leur calendrier de vaccination.

Tous les nourrissons devraient recevoir leur première dose de vaccin anti-hépatite B dès que possible après la naissance, de préférence dans un délai de 24 heures. S'il n'est pas possible de respecter ce délai, la dose à la naissance reste efficace pour prévenir la transmission périnatale si elle est administrée dans les 7 premiers jours de vie, en particulier dans les 3 premiers jours. Toutefois, elle sera moins efficace que si elle avait été administrée dans un délai de 24 heures, l'efficacité du vaccin diminuant pour chaque jour écoulé. Même après 7 jours, une dose à la naissance administrée tardivement peut être efficace pour prévenir la transmission horizontale et demeure donc avantageuse. C'est pourquoi le SAGE recommande que tous les nourrissons reçoivent la dose à la naissance lors de leur première visite dans un établissement de santé, à tout moment jusqu'à la première dose de primovaccination. Si elle est administrée après 24 heures, elle sera consignée en tant que dose tardive à la naissance.

La dose à la naissance devra être suivie de 2 ou 3 autres doses pour achever la série de primovaccination. Les 2 options suivantes sont convenables:

- (i) schéma à 3 doses de vaccin anti-hépatite B, avec administration de la première dose (monovalente) à la naissance et administration des deuxième et troisième doses (vaccin monovalent ou combiné) au même moment que la première et la troisième dose du vaccin DTC; ou
- (ii) schéma à 4 doses, avec administration d'une dose monovalente à la naissance, suivie de 3 doses de vaccin monovalent ou combiné, généralement administrées en même temps que d'autres vaccins du programme de vaccination systématique des nourrissons.

Le SAGE n'a pas proposé de modification des recommandations actuelles relatives aux doses de rappel, à l'intervalle entre les doses ou à la vaccination de groupes particuliers, comme les personnes infectées par le VIH, les nourrissons en insuffisance pondérale à la naissance et les personnes présentant un risque accru d'exposition à l'hépatite B sur leur lieu de travail, notamment les agents de santé.

Une enquête et une revue systématique avaient été menées afin d'identifier les obstacles à l'administration de la dose à la naissance.

SAGE recognizes that in some countries a substantial number of births still occur out of health facilities and this can hinder timely administration of a birth dose since the vaccine should be kept in the cold chain and therefore may not be available at the birth site.

All producers of prequalified hepatitis B vaccine had been requested to provide information on their vaccine's thermostability so that SAGE could assess whether to support the use of the vaccine out of the cold chain for infants born outside health-care settings. The data suggest that the reviewed hepatitis B vaccines are thermostable for at least 4 weeks at temperatures of 37 °C and 40–45 °C. Two manufacturers indicate on the label that the vaccine maintains potency for a month at 37 °C, though they currently recommend storage at 2–8 °C.

SAGE strongly urges all the pre-qualified vaccine manufacturers of monovalent hepatitis B vaccine to pursue regulatory approval for Controlled Temperature Chain (CTC) as soon as possible, given the available evidence of compatibility with CTC requirements.

In the interim, SAGE supports countries that choose to pursue an out of cold chain policy for a given monovalent hepatitis B vaccine and strongly recommends that when doing so they should follow the current IPAC recommendations for out of cold chain and CTC use of vaccines.¹⁸

Schedules and strategies for human papillomavirus (HPV) immunization

SAGE was presented with updated evidence on the burden related to HPV, HPV vaccines, impact of HPV immunization programmes, and modelling of the impact of HPV immunization schedules and strategies. The focus was on evidence relevant to low and middle income countries where a large proportion of global cervical cancer cases and deaths occur.

Current evidence suggests that the 3 registered vaccines (2, 4 and 9-valent) offer relatively similar effectiveness for the prevention of cervical cancer. This has to do with the fact that HPV 16/18 (against which all 3 available vaccines afford specific protection) are associated with 71% of the cases. HPV31/33/45 (3 types against which the 2-valent and 4-valent vaccines are reported to give cross protection) are associated with a further 13% of cases and HPV 31/33/45/52/58 altogether (against which the 9-valent vaccine affords specific protection) are associated with 18% of the cases i.e. a further 5% compared with HPV 31/33/45.

SAGE recommends that the priority of HPV immunization should remain the prevention of cervical cancer which is shown to be best achieved through the immunization of girls, prior to sexual debut.

Le SAGE est conscient que dans certains pays, le nombre de naissances ayant lieu hors des établissements de santé demeure important, ce qui peut empêcher l'administration rapide d'une dose à la naissance car le vaccin doit être conservé dans la chaîne du froid et n'est donc pas nécessairement disponible sur le lieu de la naissance.

Il a été demandé à tous les fabricants de vaccins préqualifiés contre l'hépatite B de fournir des informations sur la thermostabilité de leur vaccin pour permettre au SAGE de déterminer s'il serait acceptable d'utiliser le vaccin en dehors de la chaîne du froid pour vacciner les nourrissons nés en dehors des structures de santé. Les données semblent indiquer que les vaccins contre l'hépatite B étudiés sont thermostables pendant au moins 4 semaines à des températures de 37 °C et 40-45 °C. Deux fabricants précisent sur l'étiquette que leur vaccin conserve son activité pendant un mois à 37 °C, bien que la température de conservation actuellement recommandée soit de 2-8 °C.

Le SAGE invite instamment les fabricants de vaccins monovalents préqualifiés contre l'hépatite B à s'efforcer d'obtenir dès que possible une approbation réglementaire pour l'utilisation de leur vaccin dans la chaîne à température contrôlée (CTC), compte tenu des données disponibles démontrant leur compatibilité avec les exigences de la CTC.

En attendant, le SAGE soutiendra les pays qui décident d'appliquer une politique d'administration en dehors de la chaîne du froid d'un vaccin monovalent particulier contre l'hépatite B et leur recommande vivement, ce faisant, de respecter les recommandations actuelles de l'IPAC quant à l'utilisation des vaccins en dehors de la chaîne du froid et dans la chaîne à température contrôlée.¹⁸

Schémas et stratégies de vaccination contre le papillomavirus humain (PVH)

Le SAGE a pris connaissance des données les plus récentes sur la charge du PVH, les vaccins anti-PVH, l'impact des programmes de vaccination contre le PVH et la modélisation de l'impact des schémas et stratégies de vaccination contre le PVH. Il a principalement porté son attention sur les informations relatives aux pays à revenu faible ou intermédiaire, où se concentre une forte proportion des cas de cancer du col utérin et des décès associés dans le monde.

Les données actuelles semblent indiquer que les 3 vaccins homologués (bivalent, quadrivalent et nonavalant) présentent une efficacité plus ou moins comparable pour la prévention du cancer du col de l'utérus. Cela s'explique par le fait que les PVH 16/18 (contre lesquels les 3 vaccins disponibles confèrent tous une protection spécifique) sont à l'origine de 71% des cas. Les PVH 31/33/45 (3 types contre lesquels une protection croisée a été signalée avec les vaccins bivalent et quadrivalent) représentent 13% des cas et, pris dans leur ensemble, les PVH 31/33/45/52/58 (contre lesquels le vaccin nonavalant offre une protection spécifique) sont associés à 18% des cas, soit 5% de plus que les PVH 31/33/45.

Le SAGE recommande que la prévention du cancer du col utérin demeure l'objectif prioritaire de la vaccination anti-PVH. Il a été démontré que la vaccination des jeunes filles avant les premiers rapports sexuels est le meilleur moyen d'atteindre cet objectif.

¹⁸ See http://www.who.int/immunization/programmes_systems/policies_strategies/ipac/en/

¹⁸ Voir http://www.who.int/immunization/programmes_systems/policies_strategies/ipac/en/

While the experience in demonstration projects has been valuable, SAGE recommends that countries now proceed with nationwide introduction of HPV vaccines. Phased introductions should only be an alternative for countries where financial or operational constraints prevent an immediate country-wide immunization programme.

SAGE noted that reaching high vaccination coverage in girls also results in herd protection for boys, which illustrates the importance of prioritizing high HPV vaccination coverage in adolescent girls. When the coverage in girls is $\geq 80\%$, gender-neutral vaccination including adolescent boys is less cost-effective than when targeting only girls and women aged 9–18 years. At lower levels of coverage, vaccination targeting only girls and women aged 9–18 years is still likely to be more cost-effective than gender-neutral vaccination.

Nonetheless, SAGE also recognized that gender-neutral immunization could be considered based on elements such as disease burden, sexual behaviour in a country, equity, programmatic implications, cost-effectiveness, and affordability.

SAGE noted that, due to estimated larger direct protection and stronger herd effects, immunization targeting multiple age cohorts between 9 and 18 years would result in faster and larger 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 any interruptions in vaccine delivery.

Immunization of multiple cohorts of girls is cost-effective in the age range 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 the proportion of sexually active females is larger in this older age cohort.

SAGE recommends that HPV vaccine be promptly introduced for young girls as part of a coordinated and comprehensive strategy to prevent cervical cancer and other diseases caused by HPV, in accordance with the guidance in the 2014 HPV position paper.¹⁹ The immunization of multiple cohorts of girls aged 9–14 years is recommended when the vaccine is first introduced. If resources are available, the age range could be expanded up to 18 years. HPV vaccine introductions based on single or multiple age cohorts will require adequate operational and financial planning.

Bien que les projets pilotes aient été porteurs de précieux enseignements, le SAGE recommande que les pays procèdent désormais à l'introduction des vaccins anti-PVH à l'échelle nationale. L'introduction par étapes ne devrait être envisagée que dans les pays où des contraintes financières ou opérationnelles empêchent le déploiement immédiat d'un programme de vaccination à l'échelle du pays.

Le SAGE a constaté qu'une couverture vaccinale élevée chez les filles se traduit également par une protection collective chez les garçons, signe qu'il est important d'accorder la priorité à l'obtention d'une forte couverture par le vaccin anti-PVH chez les filles adolescentes. Si la couverture chez les filles est $\geq 80\%$, la vaccination présente un rapport coût-efficacité plus faible lorsqu'elle est réalisée chez les deux sexes, y compris les garçons adolescents, que lorsqu'elle cible uniquement les filles et les femmes de 9-18 ans. À des taux de couverture plus faibles, le rapport coût-efficacité de la vaccination ciblant uniquement les filles et les femmes de 9-18 ans reste probablement supérieur à celui de la vaccination chez les deux sexes.

Toutefois, le SAGE a également reconnu que la vaccination chez les deux sexes pourrait être envisagée en tenant compte de facteurs tels que la charge de morbidité, les comportements sexuels dans le pays, l'équité, les incidences programmatiques, le rapport coût-efficacité et l'accessibilité économique.

Le SAGE a fait valoir qu'en raison de la protection directe plus étendue et des effets d'immunisation collective plus forts qu'elle devrait engendrer, la stratégie vaccinale consistant à cibler plusieurs cohortes d'âge entre 9 et 18 ans aurait un impact plus rapide et plus important que la vaccination d'une cohorte d'âge unique. Elle devrait aussi permettre de réaliser des économies d'échelle et pourrait rendre les programmes plus résilients à d'éventuelles interruptions de la distribution des vaccins.

La vaccination de plusieurs cohortes de jeunes filles présente un bon rapport coût-efficacité dans la tranche d'âge de 9-14 ans, en particulier lorsque le schéma étendu à 2 doses recommandé est appliqué. Le gain différentiel obtenu, en termes de rapport coût-efficacité, pour chaque nouvelle cohorte d'âge de filles et de femmes de ≥ 15 ans dépend du contexte national car un schéma de vaccination à 3 doses est nécessaire et la proportion de femmes sexuellement actives est plus importante dans cette cohorte d'âge plus avancé.

Le SAGE préconise l'introduction rapide du vaccin anti-PVH dans le calendrier vaccinal des jeunes filles, initiative s'inscrivant dans le cadre d'une stratégie complète et coordonnée de prévention du cancer du col utérin et d'autres maladies liées au PVH, conformément aux orientations fournies dans la note de synthèse de 2014 de l'OMS concernant les vaccins contre le PVH.¹⁹ La vaccination de plusieurs cohortes de jeunes filles âgées de 9-14 ans est recommandée lors de l'introduction du vaccin. Sous réserve de disponibilité des ressources nécessaires, cette tranche d'âge peut être étendue jusqu'à 18 ans. L'introduction du vaccin anti-PVH, que ce soit auprès d'une cohorte d'âge unique ou de plusieurs cohortes d'âge, suppose une planification opérationnelle et financière adéquate.

¹⁹ See No. 43, 2014, pp. 465–491.

¹⁹ Voir N° 43, 2014, pp. 465-491.

Yellow fever

Recent outbreaks of YF in Central Africa, including in urban areas, highlighted the need to revisit and expand the control strategy and the vaccine supply, as well as the need for increasing vaccine supply surge capacity. Therefore, WHO has initiated the development of a new global strategy to Eliminate Yellow Fever Epidemics (EYE strategy) by 2026, with 3 strategic objectives: protect at-risk populations, prevent international spread, and rapidly contain outbreaks. Where the risk is high, the protection of the at-risk populations includes vaccination of everyone through preventive mass vaccination campaigns and, as necessary, catch-up campaigns, the inclusion of YF vaccination in routine immunization schedules for children and improving routine immunization performance. The strategy outlines 4 key requirements: continued access to affordable vaccines through a sustainable vaccine market; political commitment at global, regional and country levels; robust governance and strong partnerships; and research to support better tools and practices. New features of the strategy include the revised country risk category, the aim to protect specific risk populations, the need to address the urban risk, and the establishment of a revolving emergency vaccine stockpile. Following establishment of the EYE strategy, WHO and partners will proceed with developing an implementation plan.

SAGE supported the general approach of the EYE strategy and emphasized the importance of linking the EYE strategy to existing programmes/initiatives, e.g. measles-rubella strategy, integrated disease surveillance, and also vector control. It was noted that EYE can serve as a driver to raise awareness and preparedness in urban settings for other outbreak prone diseases.

SAGE requested more rationale to justify the recommendation against implementing preventive vaccination in countries classified in the moderate risk category, given the occurrence and rapid spread of other *Aedes*-borne diseases. While priority is given to tackling the risk where it is known and lowering it at the source, YF vaccination is not without risk and should always be considered in the context of the vaccine's risk/benefit profile. The small margin of difference between the predicted vaccine demand and expected maximum supply capacity calls for careful planning and execution of the EYE strategy. According to the risk, EYE implementation should be considered for the national or subnational levels.

Considering the global spread of *Aedes* mosquitos, rapid urbanization and increased international travel, surge capacity in the event of an outbreak is needed to extend the supply beyond that of the available stockpile. SAGE previously reviewed the evidence for the minimum effective dose (fractional dose) in June 2016 in the context of the outbreak in Central Africa and supported its use in that context. The minimum effective fractional

Fièvre jaune

Les récentes flambées de fièvre jaune apparues en Afrique centrale, y compris dans des zones urbaines, ont attiré l'attention sur la nécessité de réévaluer et d'étendre la stratégie de lutte contre cette maladie et l'approvisionnement en vaccins anti-mariques, ainsi que la nécessité d'accroître les capacités de renfort de l'approvisionnement en vaccins. En conséquence, l'OMS a commencé à élaborer une nouvelle stratégie mondiale d'élimination de l'épidémie de fièvre jaune (stratégie «EYE», de l'anglais «Eliminate Yellow Fever Epidemics») à l'horizon 2026, axée sur 3 objectifs stratégiques: protéger les populations à risque, prévenir la propagation internationale de la maladie et endiguer rapidement les flambées. Dans les zones où le risque est élevé, la protection des populations à risque suppose entre autres de vacciner toutes les personnes au moyen de campagnes préventives de vaccination de masse et, au besoin, de campagnes de rattrapage, d'inclure la vaccination anti-marique dans les calendriers de vaccination systématique des enfants et d'améliorer la performance des programmes de vaccination systématique. La nouvelle stratégie définit 4 conditions essentielles: accès durable aux vaccins à un prix abordable dans le cadre d'un marché viable des vaccins; engagement politique aux niveaux mondial, régional et national; gouvernance et partenariats solides; et activités de recherche pour la mise au point d'outils et de pratiques améliorés. Parmi les nouveaux éléments de cette stratégie figurent: une catégorisation révisée des pays selon le risque, la protection ciblée de populations à risque particulières, la nécessité de pallier au risque en milieu urbain, et la constitution d'un stock renouvelable de vaccins pour les urgences. Une fois la stratégie EYE établie, l'OMS et ses partenaires élaboreront un plan de mise en œuvre.

Le SAGE a soutenu l'approche générale de la stratégie, soulignant qu'il sera important de la relier aux initiatives et programmes existants, comme la stratégie de lutte contre la rougeole et la rubéole, la surveillance intégrée des maladies et la lutte antivectorielle. Il a indiqué que la stratégie pourra donner une impulsion aux efforts de sensibilisation et de préparation des zones urbaines à l'égard d'autres maladies à tendance épidémique.

Le SAGE a demandé une justification plus étoffée de la recommandation contre la mise en œuvre de la vaccination préventive dans les pays classés dans la catégorie de risque modéré, compte tenu de la présence et de la propagation rapide d'autres maladies transmises par le moustique *Aedes*. Bien que l'objectif prioritaire soit de pallier au risque là où il est identifié et de le réduire à la source, la vaccination anti-marique n'est pas sans risque et doit toujours être envisagée en tenant compte du profil risque/bénéfice du vaccin. Le léger écart entre la demande prévue en vaccins et la capacité maximale d'approvisionnement escomptée impose une planification et une exécution attentives de la stratégie EYE. Selon le risque, la mise en œuvre de la stratégie sera envisagée aux niveaux national ou infranational.

Compte tenu de la prolifération mondiale des moustiques du genre *Aedes*, de l'urbanisation rapide et de l'intensification des voyages internationaux, une capacité de renfort en cas de flambée est nécessaire pour étendre l'approvisionnement au-delà des stocks existants. En juin 2016, dans le cadre de la flambée survenue en Afrique centrale, le SAGE avait examiné les données relatives à la dose minimale efficace du vaccin (dose fractionnée) et s'était prononcé en faveur de son utilisation dans ce

dose, administered as a fraction of the volume of the normal standard dose, should induce a protective immune response equivalent to that induced by a full standard dose. SAGE was updated on the evidence for a minimum effective fractional dose, most of which is limited to one of the YF vaccine products. Available studies suggest that a reduced volume dose was equivalent to a standard dose with respect to all measured immunological and virological parameters, provided the dose contained ≥ 3000 international units.

SAGE was also updated on the experience of the fractional dose campaign in Kinshasa in August 2016. At that time, there was a target population of 10.5 million people in Kinshasa and bordering zones, with only 5.8 million doses available. A fractional dose (1/5 volume of a standard dose) was administered to all individuals in Kinshasa, except for children aged < 2 years and pregnant women who received a standard dose. Logistically and operationally, the use of a fractional dose was shown to be feasible and a promising approach to protect at-risk populations that would otherwise be left unprotected.

Based on the available evidence, SAGE reaffirmed that a fractional dose can be used as part of an exceptional response when there is a large outbreak and a shortage of vaccine. Preference should be given to vaccines for which immunogenicity data on a fractional dose are available. Constituting an off-label use of the vaccine and not meeting current YF vaccination requirements under the International Health Regulations (IHR), it should be confined to outbreak responses when vaccine is in short supply. Determining what the most suitable volume (1/2 or 1/5 of a standard dose) to be used as a fractional dose should be done in conjunction with WHO with consideration of the available vaccine product. This dose should be administered according to the standard administration route. In the absence of additional data, children aged < 2 years, pregnant women and HIV-infected individuals should be offered a standard dose. While available clinical trial data do not suggest a need for revaccination after receipt of a fractional dose, monitoring of immunogenicity, duration of immunity and vaccine failures is needed to substantiate this assumption.

Although there is evidence to support fractional dosing in adults with one product, there are important research gaps that must be addressed to allow for flexibility in the use of fractional doses during severe vaccine shortages. Taking a near-term and pragmatic approach, SAGE prioritized head to head non-inferiority studies of all 4 WHO prequalified YF vaccines, as well non-inferiority studies in special populations. Of particular importance, given the consequences for international travel involving IHR requirements is the duration of protection with fractional dosing, including the potential need for revaccination. Safety and effectiveness assessments should be put in place when minimal effective doses are used. ■

contexte. La dose fractionnée minimale efficace, administrée sous forme de fraction volumique de la dose standard normale, devrait induire une réponse immunitaire équivalente à celle d'une dose complète standard. Des données actualisées sur la dose fractionnée minimale efficace ont été présentées au SAGE, se limitant essentiellement à l'un des produits vaccinaux contre la fièvre jaune. Les études disponibles indiquent qu'une dose volumique réduite équivaut à une dose standard pour tous les paramètres immunologiques et virologiques mesurés, tant qu'elle contient ≥ 3000 unités internationales.

Le SAGE a également pris connaissance des informations les plus récentes sur l'utilisation de la dose fractionnée dans le cadre d'une campagne à Kinshasa en août 2016. Au moment de la campagne, la population ciblée, à Kinshasa et dans les environs, s'élevait 10,5 millions de personnes et seules 5,8 millions de doses étaient disponibles. Une dose fractionnée (correspondant à 1/5 du volume de la dose standard) a été administrée à tous les habitants de Kinshasa, à l'exception des enfants de < 2 ans et des femmes enceintes, lesquels ont reçu une dose standard. Sur le plan logistique et opérationnel, l'utilisation de la dose fractionnée s'est révélée réalisable et cette approche s'est avérée prometteuse pour protéger des populations à risque qui n'auraient pas pu, sinon, bénéficier de cette protection.

Au vu des données disponibles, le SAGE a réaffirmé qu'une dose fractionnée peut être utilisée dans le cadre d'une riposte exceptionnelle à une flambée de grande ampleur en cas de pénurie de vaccins. La préférence sera accordée aux vaccins pour lesquels on dispose de données sur l'immunogénicité d'une dose fractionnée. Cette approche constitue une utilisation hors indication du vaccin et ne remplit pas les conditions actuelles d'utilisation du vaccin anti-marijuana au titre du Règlement sanitaire international (RSI). Elle doit donc se limiter aux situations de riposte à une flambée en cas de pénurie de vaccins. Le volume adéquat à utiliser pour la dose fractionnée (1/2 ou 1/5 de la dose standard) devra être déterminé en concertation avec l'OMS et en tenant compte du produit vaccinal disponible. Cette dose devra être administrée selon la voie d'administration standard du vaccin. En l'absence de données supplémentaires, les enfants de < 2 ans, les femmes enceintes et les personnes infectées par le VIH devront se voir offrir une dose standard. Les données d'essais cliniques disponibles n'indiquent en rien qu'il soit nécessaire de procéder à une revaccination après l'administration d'une dose fractionnée, mais il est indispensable de surveiller l'immunogénicité, la durée de l'immunité et les échecs de la vaccination pour étayer cette hypothèse.

Bien que l'on dispose de données favorables à l'utilisation de doses fractionnées chez l'adulte pour l'un des produits, d'importantes lacunes persistent en matière de recherche. Ces dernières devront être comblées pour permettre une utilisation plus souple des doses fractionnées en cas de graves pénuries en vaccins. Optant pour une approche pragmatique axée sur le court terme, le SAGE a accordé la priorité aux études comparatives directes de non-infériorité des 4 vaccins anti-marijuana préqualifiés, ainsi qu'à des études de non-infériorité dans certaines populations spécifiques. Compte tenu des conséquences que cela peut avoir sur les voyages internationaux soumis aux exigences du RSI, il est particulièrement important d'évaluer la durée de la protection conférée par les doses fractionnées, et notamment la nécessité d'une revaccination éventuelle. Toute utilisation de doses efficaces minimales devra s'accompagner d'évaluations de la sécurité et de l'efficacité vaccinales. ■

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 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 all regions agreed to collect and submit to HQ district level coverage data (numerator, denominator and coverage from DTP1, DTP3 and MCV1) as part of annual data collection exercise. We are exploring ways to analyse and visualise the data.
General	SAGE recommended strengthening national vaccination programs, integrating health services and strengthening health systems to promote universal health coverage.	Apr 2013	Completed	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 Expanded Programme on Immunization (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 Apr 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 Oct 2015. At the Apr 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 recommended that ways to improve curricula for medical personnel should be explored.	Nov 2008	Ongoing	The Regional Office for Africa (AFRO) has published the pre service curriculum and efforts are being made to disseminate the findings and ensure that medical and nursing schools change their outdated curriculum. This is a long process but few steps that started in that direction.

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	<p>Advice was sought from the Expert Committee on Biological Standardization (ECBS), and added to the agenda of meeting on 15-19 Oct 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.</p> <p>During the Nov 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.</p> <p>Guidelines on procedures and data requirements for changes to approved vaccines were adopted by ECBS in Oct 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 was prepared, taken through public consultation, finalized and adopted by ECBS in Oct 2016. The document can be found here: http://www.who.int/biologicals/expert_committee/Label_after_ECBS_HK_28_Oct_2016_clean.pdf?ua=1</p> <p>A paper clarifying the differences between regulatory decisions and public health recommendations was commissioned. Unfortunately, there were delays in finalization of the publication but the paper has finally been published in Vaccine and is available online with open access www.sciencedirect.com/science/article/pii/S0264410X17302694.</p>
AEFI reporting	SAGE urged that efforts be pursued to enhance Adverse Events Following Immunization (AEFI) reporting worldwide.	Apr 2016	Ongoing	<p>With Gavi support, 30 African countries have established work plans. A first analysis of the new Global Vaccine Action Plan (GVAP) indicator for Adverse events following immunization (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.</p> <p>A manuscript is currently submitted that describes the AEFI reporting ratio through Joint Reporting Form (JRF).</p>
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	<p>The Global Advisory Committee on Vaccine Safety (GACVS) concluded that signals documented by the Uppsala Monitoring Centre (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 United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), given their extensive experience and access to more complete information with the Individual Case Safety Reports (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.</p> <p>UMC revised its signal assessment guideline in April 2015. In March 2016, UMC was recommended to establish a review group for the vaccine signals.</p> <p>So far this has not happened though and new signals are being generated. The WHO Essential Medicines and Health Products (EMP) Department is currently examining the issue. During a recent visit to Uppsala, a reply from UMC Director was requested by the WHO Safety and Vigilance team.</p>

Topic	Recommendations/Action Item	Meeting Date	Status	Comments and Follow up
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	Closed-not implemented	The recommendation made at the Oct 2015 SAGE meeting arrived too late to be included to the Davos 2016 agenda. Therefore, it has been agreed upon with Decade of Vaccines (DoV) partner agencies to include at World Economic Forum in Davos in Jan 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 Oct 2016). This topic has been discussed with the Bill & Melinda Gates Foundation (BMGF) in June during which a principle agreement has been reached. A concept note detailing the objectives, message and format of a possible Davos session were developed by WHO to engage the discussion but it was finally decided by WHO and the BMGF not to have the event. Focus is rather on the organization of a DoV leadership meeting in Apr 2017 which is in active preparations through discussions between the 5 lead agencies.
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 Decade of Vaccines (DoV) Working Group (WG) continues to review the need for reformulation of the indicators and mechanisms for data collection. In 2016 the WG has specifically discussed safety and demand side indicators as well as discussed indicators to be used as part of the Sustainable Development Goals (SDGs). The SAGE report of progress with the Global Vaccine Action Plan (GVAP) for 2016 i.e. the midterm progress report 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 Jan 2017 together with a draft GVAP resolution sponsored by Australia, Brazil and Colombia. A teleconference of the SAGE WG took place on 27 Mar 2017 with specific focus on the selection of the SDGs indicator for immunization (3.8), on discussing data quality and on selecting priority countries for the 2017 GVAP Secretariat report. The SAGE DoV WG will meet from 29-31 August for the yearly revision of progress in the implementation of GVAP for the year 2016.
Diphtheria	SAGE expressed its deep concern over the reported lack of diphtheria antitoxin and encouraged WHO to take on a strong leadership role in resolving this shortage globally.	Oct 2016	Ongoing	A session will be held at the upcoming April 2017 SAGE meeting which will tackle the issue of diphtheria antitoxin supply shortages.
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	SAGE established an Ebola working group (WG) in Nov 2014 which met regularly via teleconference as well as during a face-to-face meeting on the 9-10 Mar 2015. The WG reviewed the 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 Apr 2015 meeting. The WG met again on 19-20 Aug 2015 to review the available information and to start framing recommendations, based on the framework approved by SAGE in Apr 2015. The WG input was presented to SAGE at the Oct 2015 meeting. Now, that the final results of the Ring trial have been published in the Lancet in Dec 2016, a WG meeting will take place 14-15 Mar 2017 to discuss the results. Regulatory evaluation of the vaccine is currently ongoing. There is information regarding a Russian developed vaccine that was licensed in Russia, but despite WHO requests no detailed data is available. The emerging data and draft recommendations were discussed during the face to face meeting of the WG which took place Mar 2017. The WG will present to SAGE in Apr 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 Mar 2017.</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 resulted in an enhanced vigilance in the country. As exemplified by the outbreak in San Martín, the risk persists in the population. 73% of hepatitis A virus (HAV) acute infection cases reported occurred in individuals over >10 years. All cases reported occurred in unvaccinated individuals.</p> <p>After now 11 years of follow-up, there is currently still no evidence of waning immunity and the outbreak experienced in 2014 was compatible with very high vaccine effectiveness. Hepatitis A cases have remained low in 2014, 2015, and 2016. 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.</p> <p>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.</p> <p>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. The results of the phase 2 study conducted in 2013 with a median post-vaccination interval of 7.7 years were quite reassuring with a prevalence of protective antibodies of 97.4% (95% CI: 96.3-98.3) still protected. More recent analysis (phase 3) indicates that the prevalence of protective antibodies in children > 9 years following a single dose of hepatitis A vaccine was still 87.6% but a decrease was observed in all centers with decreased GMCs. It is still unclear if different samples or differences in methodology or recall bias in seronegative individuals could actually account for the difference, but this requires continued follow up. For the time being epidemiologic surveillance continues to show very low infection rates in all regions and age groups with sporadic cases occurring mainly in frontier regions and non-vaccinated adolescents.</p>
Hepatitis B	SAGE strongly urges all the pre-qualified vaccine manufacturers of monovalent hepatitis B vaccine to pursue regulatory approval for Controlled Temperature Chain (CTC) as soon as possible, given the available evidence of compatibility with CTC requirements.	Oct 2016	Ongoing	To date, WHO has not received any application from hepatitis B vaccine manufacturers to support the label change of prequalified hepatitis B vaccine.

Topic	Recommendations/Action Item	Meeting Date	Status	Comments and Follow up
Hepatitis B	<p>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.</p>	Apr 2009	Ongoing	<p>A new indicator for Hepatitis B birth dose has been added to the WHO /UNICEF Joint Reporting Form (JRF), 2017 - this new indicator will allow the distinction between timely (24 hours) and late birth dose administration.</p> <p>In Nov 2016, AFRO held consultation on hepatitis B control and included discussing barriers, actions and support needed towards hepatitis B birth dose introduction. This was part of joint meeting held with viral hepatitis counterparts.</p> <p>A consultation on implementation of a new universal birth dose recommendation was conducted in Dec 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 Apr 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 Mar 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 Dec 2015. Senegal held a Hepatitis B birth dose training workshop in Dec and introduced birth dose in Jan 2016.</p> <p>Guidance for hepatitis 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/ in English, French and Spanish. An Arabic version is under development). The guidance includes a chapter on reporting and monitoring birth dose vaccination.</p> <p>In July 2016, a proposal to revise WHO/UNICEF 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	<p>As of Jan 2017, all regions have had the regional committees (RCs) on immunization endorse hepatitis B control goals, except for the South East Asian Regional Office (SEARO) which as noted below had a 2016 ITAG recommendation to establish a goal. Regional goals slightly differ in target dates, threshold prevalence and specific ages in which to measure prevalence - but are largely similar nonetheless.</p> <p>In Sept 2016, the European Regional Office (EURO) held a consultation to discuss establishing a regional verification mechanism.</p> <p>In June 2016, the 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.</p> <p>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.</p> <p>The Eastern Mediterranean Region (EMR) has a 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.</p> <p>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.</p> <p>The EURO will consider a regional hepatitis B control goal as proposed by ETAGE.</p> <p>The Pan American Health Organization (PAHO) has resolved to eliminate hepatitis B virus transmission and is formulating a regional strategy.</p> <p>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.</p> <p>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).</p> <p>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.</p>

HIV	SAGE requested regular updates on the progress of HIV-vaccine research.	Apr 2010	Ongoing	<p>The recent start of a phase 2b 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 favorable results from a 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. WHO IVR is considering the value of organizing a consultation on preparation for success, downstream access and use.</p>
-----	---	----------	---------	--

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>The funding grant from Bill & Melinda Gates Foundation (BMGF) for schedules-related work to inform SAGE discussions on immunization schedules is now over. All delays in regard to this work were due to the Ebola outbreak and the R&D Blueprint on staff responsibilities.</p> <ul style="list-style-type: none"> - Pneumococcal Conjugate Vaccine (PCV): evidence was reviewed by SAGE in November 2011. A new position paper was published in 2012. - 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 was published in February 2013. A new review of evidence is ongoing. - Haemophilus influenzae type b (Hib): The issue was revised during the April SAGE 2013 meeting. A new position paper was issued. - Pertussis: evidence was reviewed by SAGE in 2015. A new position paper was issued. - Hepatitis B: evidence was reviewed by SAGE in Oct 2016. A new position paper is expected in 2017. - HPV: evidence was reviewed by SAGE in Oct 2016. A new position paper is expected in April 2017. - TT vaccine: evidence was reviewed by SAGE in Oct 2016. A new position paper is expected in 2017. February 2017 - Diphtheria: evidence will be reviewed by SAGE in Apr 2017. A new position paper is expected in 2017. <p>A consultation to develop analytic tools to support countries with the selection and/or adjustment of vaccine schedules in different epidemiological and operational scenarios took place in December 2016.</p>
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	<p>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.</p>
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	<p>WHO is currently implementing multiple World Health Assembly (WHA) resolutions that mandate integration of disease-specific programs, using a Health Systems Strengthening (HSS) framework. This aims to seek universal immunization coverage as part of Universal health coverage (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 Health Systems and Innovation (HIS)/Health Sys Governance, Policy & Aid Effectiveness (HGS) has assisted the Gavi Alliance Partners and Gavi Secretariat in developing.</p>

Topic	Recommendations/Action Item	Meeting Date	Status	Comments and Follow up
Implementation	SAGE recommended the formation of an implementation group that had a broad array of expertise in this area.	Apr 2015	Closed	<p>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.</p> <p>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.</p>
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	<p>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.</p>
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	<p>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 (NSE) 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 Feb 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.</p> <p>At the Feb 2017 meeting IVIR-AC reviewed the final proposals for 2 trial designs suggested by the ad-hoc Working Group on NSE. It will be presented at the SAGE Apr 2017 meeting as part of the briefing of IVIR-AC by chair Rob Breiman.</p>

Topic	Recommendations/Action Item	Meeting Date	Status	Comments and Follow up
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. 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. The global pertussis estimates for age under 5 will be published soon in Lancet Infectious Diseases.</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/published by Q2-2017. These include: a planning guide, the assessment methodology (including the MOV protocol, sample questionnaires and generic field guides) and an intervention guidebook. In the meantime, WHO has launched a web page with the DRAFT guidelines for easy access.</p> <p>Having strengthened the capacity of AFRO to implement MOV assessments (in Chad, Malawi and Kenya; planning phases for DRC, Nigeria, and Mauritania), 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 Cambodia (WPRO, in collaboration with CDC). To establish a network of partners engaged in MOV, an informal coordination meeting was established in March 2016 to provide regular briefing on the process and outcomes of the recent country MOV assessments, share future plans and framework for implementation, exchange lessons learned, and achieve consensus on a coordination mechanism for all MOV work among all partners. The third partner coordination call took place on January 26, 2017, to elicit opportunities to collaborate on upcoming country activities. WHO contracted one of the partners (AMP) to lead the assessment in Burkina Faso. WHO is planning a partner training on the MOV methodology for Q2-2017, to enable more rapid scale up of impact.</p>

Topic	Recommendations/Action Item	Meeting Date	Status	Comments and Follow up
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	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. 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. 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.
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	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. At the February 2017 meeting IVIR-AC reviewed the final proposals for 2 trial designs suggested by the ad-hoc working group on NSE. It will be presented at the SAGE April 2017 meeting as part of the briefing of IVIR-AC by the chair, Rob Breiman.
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	Closed	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).

Topic	Recommendations/Action Item	Meeting Date	Status	Comments and Follow up
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 endorsement of the MIC Strategy in Apr 2015, the WHO-led MIC Task Force initiated a country engagement process: in collaboration with key immunization partners WHO started multi-partner dialogues with four countries struggling with raising or maintaining high immunization coverage and/or introducing new vaccines. With each of these countries, the MIC Task Force has identified obstacles to achieving and sustaining the immunization system performance and potential solutions to reaching GVAP targets through plans of action. The MIC Task Force selected four countries for the MIC strategy implementation based on potential for impact (birth cohort, coverage of traditional vaccines, status of new vaccines introduction) and feasibility of engagement. Selected countries are Romania, Swaziland, Jordan and Philippines. Countries are at different stages of implementation of their plan of actions.</p> <p>Also, some efforts to support all MIC countries in the area of access to timely and affordable supply have been implemented. Notably, the creation of a mechanism for access to supply in humanitarian emergencies in MICs not supported by Gavi; set up of a peer platform and regional workshop to strengthen country procurement capacity; work on price transparency continues successfully with 70% of world (n. of countries and birth cohort) sharing vaccine product, price and procurement information since the beginning of WHO price transparency efforts. Despite these efforts, progress in implementation of the strategy across its 4 pillars is very slow due to lack of funding. As discussed at the Apr 2015 SAGE meeting, the partners would require about US\$20M per year to fully implement the strategy.</p> <p>In Oct 2016, a meeting of the MIC Task Force was held to review progress and discuss next steps. The TF determined having concluded its mandate through a review of the MIC issue and the development of a partner-shared MIC strategy. It was thus proposed that the TF comes to a close. As it close, the MIC TF made the following recommendations:</p> <p>1- The TF expressed important concerns regarding funding for implementation of the MIC Strategy and called for fundraising efforts by its member organisations or other appropriate coalition of partners. For these purposes it proposed continued awareness raising on the MIC issue through:</p> <p>A- Development of an advocacy tool to be developed starting from technical background documents prepared for the SAGE April 2015 meeting. A time limited and informal Steering Committee of some TF members (WHO, UNICEF, TFGH and other as interested) could be set up to follow work by external consultants.</p> <p>B- Regular monitoring & reporting on MIC progress against GVAP as well as monitoring of implemented activities against intended activities under the MIC strategy (dashboard).</p> <p>2-The TF agreed on the importance to ensure completion of pending tasks and enhance smooth transitioning as the TF sunsets.</p> <p>3- Anticipating that considerable time may be needed for funding to become available, the TF proposed that partners focus on i) regular normative/guidance work benefitting all countries including non Gavi MICs and ii) access to affordable and timely supply (continuing working on implementation of ongoing activities and potentially new one as possible). Partners committed to continue information sharing and collaborative spirit in these efforts.</p>

Topic	Recommendations/Action Item	Meeting Date	Status	Comments and Follow up
Malaria Vaccine	SAGE requested continued review of the planning of the pilot implementations and to receive regular updates on the results.	Oct 2015	Ongoing	In November 2016, the Global Fund to Fight AIDS, Tuberculosis and Malaria approved US\$ 15 million from its catalytic funds for the malaria vaccine pilots. Together with previous funding commitments made by Gavi, the Vaccine Alliance (up to \$27.5 million, matching other sources 1 to 1) and UNITAID (\$9.6 million) a total of \$49.2 million has now been pledged for the first four years of the Programme (2017-2020). These commitments enable the Programme to start initial visits by a joint delegation from WHO, PATH and GSK to each of the 3 shortlisted countries took place in October-November 2016. The proposed Malaria Vaccine Implementation Programme was discussed with senior representatives from the Ministry of health, including the National Malaria Control Programme, the Expanded Programme on Immunization, regulatory authorities, research organizations and partners. The visits confirmed continued interest and suitability to participate in the programme for all three countries. Kenya, Malawi and Ghana have been formally notified of their selection in February 2017. A public announcement of the country selection will be made in the coming weeks. SAGE members are requested not to reveal the country names until publication of the WHO press release. Intensive preparation activities have now started with the aim to introduce the RTS,S malaria vaccine in pilot areas in 2018. The national regulatory agencies of the 3 countries have been convened under African Vaccine Regulatory Forum (AVAREF) on 18-19 February 2017 to explore a potential joint regulatory review and shared or collaborative oversight mechanisms for RTS,S use in the pilots.
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, IVFI 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 the Regional Office for the Americas to document the successful regional experience of delivering influenza vaccine to pregnant women.	Apr 2015	Ongoing	Regarding the Regional Office for the Americas/Pan-American (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 Latin America and Caribbean Region since the pandemic, highlighting the improvements in targeting pregnant women for vaccination in 29 countries. - During 2015 PAHO conducted, a survey among 14 Latin American countries (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. - During 2016, PAHO collaborated with the Ministry of Health of Nicaragua to document factors associated with their successful expansion of influenza vaccination among pregnant women in Nicaragua in 2013. Findings from this experience were published in Vaccine in Feb 2016. - 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. Currently the maternal and neonatal immunization field guide is in the final round of editing. It will be published in English and Spanish in the course of Mar 2017. - In 2017 PAHO has been stressing, at various meetings held in country and at the regional level, the importance of offering influenza vaccines to pregnant women through routine healthcare services throughout the season, especially in tropical countries where influenza circulation tends to last.

Topic	Recommendations/Action Item	Meeting Date	Status	Comments and Follow up
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 has completed 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 has produced a document titled, "Labelling information of inactivated influenza vaccines for use in pregnant women." The document was reviewed and endorsed by Expert Committee on Biological Standardization (ECBS) in late 2016.
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	WHO's Initiative for Vaccine Research (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 adverse events following immunization surveillance guidance; and 7) implementation guidance document. IVR is collaborating with the US CDC to pilot some of these tools in low and middle income countries.
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 is expected to be completed by July 2017. 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.
Measles	SAGE supported the development by WHO of a standardized method to categorize countries based on their level of disease control and likelihood of achieving and sustaining measles and rubella elimination, and tailoring immunization and surveillance strategies to the country categorization.	Oct 2016	Ongoing	The categorization is currently being discussed by the Measles and Rubella SAGE Working Group via the monthly teleconferences and the next version will be shared with regions and regional vaccine advisory committees to ensure alignment. The final categorization will be completed and reported on at the October 2017 SAGE meeting.
Measles	SAGE stressed that the accumulation of susceptible persons at both the national and subnational level should continue to be monitored to identify and address immunity gaps. SAGE requested that the Measles and Rubella Working Group refine the recommendations as to when follow-up SIAAs should be conducted.	Oct 2016	Ongoing	The draft updated measles position paper (to be published in May 2017) stresses the importance of monitoring the accumulation of susceptible persons at both the national and subnational level to identify and address the immunity gaps. The SAGE MR Working Group is looking at refining recommendations as to when follow up supplementary immunization activities (SIAs) should be conducted and it is expected that they will report on this at the October 2017 SAGE meeting.
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) are expected to have the results from their clinical studies of the immune response to an early dose of MMFR vaccine in 2017. 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 Measles and Rubella Working Group by end of June 2017.

Topic	Recommendations/Action Item	Meeting Date	Status	Comments and Follow up
Measles	SAGE recommended that the most expeditious clinical development and regulatory pathway to licensure of measles containing vaccines (MCV) micro-array patch (MAP) be determined, and that barriers to the development, licensure, and use of MAPs for measles and rubella vaccine delivery be identified and addressed urgently.	Oct 2016	Ongoing	Pending approval of financial support, a Measles and Rubella/ micro-array patch (MAP) Working Group (WG) will be set up in 2017 to develop a clinical regulatory pathway. The outcomes and recommendations from this WG will be shared with SAGE later this year.
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 Feb 2015: http://www.who.int/wer/2015/wer3008/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, 4 countries have launched their introduction at the age of 9 months (Sudan, July 2016 and Mali, Feb 2017); at the age of 18 months (Ghana, November 2016) and at the age of 15 months (Burkina Faso, Mar 2017), respectively. The remaining four countries (Central African Republic, Chad, Niger and Nigeria) intend to do so in 2017. Another 2 countries (The Gambia and Guinea) have applied to Gavi in 2016. Other meningitis belt countries intend to apply for the introduction of the vaccine into their routine programme at the next Gavi application windows in May and Sep 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	The SAGE Secretariat has proposed reporting to SAGE in writing for the moment through the SAGE issue tracker. See other item in the SAGE tracking sheet on this topic.
MNTE	UNICEF, UNFPA and WHO should work with countries to generate and sustain political commitment to maintaining elimination of MNT, in order to guard against complacency once a country has been declared to have achieved elimination.	Oct 2016	Ongoing	All opportunities including the Regional Immunization Technical Advisory Group (RITAG) meetings and Immunization Managers' meetings are being utilized to advocate for efforts by countries to sustain their Maternal and Neonatal Tetanus Elimination (MNTE) status. MNTE was one of the few topics the African RITAG focused on during its meeting in Dec 2016. Additionally, efforts are being made to finalize the guidelines on sustaining MNTE to ensure that countries are guided through the appropriate steps to take to sustain their achievements.
MNTE	UNICEF, UNFPA, and WHO should urgently develop an MNTE investment case and resource mobilization strategy to secure predictable and timely funding support for the remaining 18 countries, if the 2020 elimination timeline is to be met.	Oct 2016	Ongoing	There is currently a collaborative work by WHO, UNICEF and The United Nations Population Fund (UNFPA) that has led to the establishment of the Terms of Reference for the work on the investment case, and the recruitment of a consultant has been finalized. The target is to complete elimination section of this work by mid year.
MNTE	WHO should re-emphasize the previous recommendations on the number of doses needed in women of reproductive age if SIAs or routine immunization of pregnant women are needed and clarify that pregnant women are protected when they have had 5–6 documented doses (by card, immunization registry and/or history) by the time of reproductive age. Updated WHO recommendations should reinforce the need for booster doses for both males and females throughout the life course, opportunistic catch-up immunization, individual and community education on clean wound care and following standard surgical protocols as per the WHO infection prevention guidelines.	Oct 2016	Completed	Following the recommendations from SAGE in October 2016, the position paper on tetanus vaccines has been revised and updated. This position paper was published in the Weekly Epidemiological Record (WER) on 10 February 2017.

Topic	Recommendations/Action Item	Meeting Date	Status	Comments and Follow up
MNTE	Where feasible, the use of serosurveys to validate assessment of risk identified 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 provide guidance on: sampling methods; sample collection and testing; and analysis, interpretation and use of serosurvey data for monitoring. WHO should consider establishing reference laboratories and reference serum panels to support standardization and quality assurance of the laboratory methods used in serosurveys.	Oct 2016	Ongoing	This recommendation has not yet progressed much as yet. We have, however, initiated discussions with CDC on the feasibility of combining some of the MNTE validation surveys with serosurvey.
MNTE	UNICEF, UNFPA, and WHO should make all efforts to secure timely supply of the available WHO pre-qualified TT 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.	Oct 2016	Ongoing	Efforts are currently going on to submit a proposal to the Gavi Alliance Policy and Programme Committee to request for financial assistance to support the production and availability of this critical device aimed at markedly increasing access to the Tetanus Toxoid vaccine to very remote parts of some selected countries where currently access is seriously compromised as a result of insecurity, active conflicts and lack of human resources.
MNTE	UNICEF, United Nations Population Fund (UNFPA), and WHO should support countries in securing the necessary resources to implement their national elimination plans, including procurement of Td vaccine and operational costs for SIAs.	Oct 2016	Ongoing	A stakeholder's meeting was convened at the end of Nov 2016 to follow up on this. Other efforts include the concept note produced to follow up on funding for Tetanus Toxoid Uniject from Gavi, the Vaccine Alliance and the work on the investment case that is anticipated to facilitate resource mobilization to help support countries to implement their elimination activities.
MNTE	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 throughout 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 aged 4 years and older.	Oct 2016	Completed	The WHO position paper on Tetanus vaccine has already been revised to reflect this recommendation on the use of age-appropriate combinations of tetanus and diphtheria toxoids. It was published in the Weekly Epidemiological Record (WER) on 10 Feb 2017. Opportunities are being used during Immunization Managers' meetings to emphasize on this.

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	Multiple injection studies have been conducted in collaboration with US CDC in South Africa, Gambia, and Albania, with studies ongoing in the Philippines, Sudan, and Columbia. Studies are primarily designed to evaluate healthcare provider and infant caregiver attitudes and practices regarding administration of multiple injectable vaccines in the same visit, in most cases following the 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, see respective tracking sheet items.
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	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. 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. 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 has been distributed to countries and the last edition was also translated into several local languages. 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. As a further example of use and integration in WHO documents, reference to the pain mitigation position paper has been made in the recently published updated tetanus position paper. 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.
Polio	SAGE requested its Polio Working Group (WG) 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	The IPV supply situation is being closely monitored. The SAGE Polio WG and SAGE issued a statement in Mar and made recommendations during the Apr 2016 SAGE meeting regarding IPV supply. This issue was further reviewed during the SAGE Polio Working Group meeting in August 2016 and during a conference call in Dec2016. An update from the meeting, including on discussions with vaccine producers, will be provided during the Apr 2017 SAGE meeting (or earlier if needed).

Topic	Recommendations/Action Item	Meeting Date	Status	Comments and Follow up
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	The 'GAPIII Containment Certification Scheme' (CCS) was endorsed by SAGE in Oct 2016 and published. The Containment Working Group (CWG) was established in Jan 2017 to support the Global Commission for the Certification of Poliomyelitis Eradication in their new global containment oversight role. WHO is now training GAPIII auditors nominated by the national authorities for containment (NACs) to assess poliovirus-essential facilities (PEFs) against the implementation of GAPIII. PEFs are expected to engage in the containment certification process, following CCS. As of Feb 2017, only 15 of 30 countries planning to retain type 2 polioviruses have nominated a national authority for containment.
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	Completed	The topic was discussed at the SAGE Polio WG in August 2016 and reported to the SAGE in October 2016. SAGE recommended that when sufficient supplies of IPV become available countries with delayed IPV introduction or stock-outs should prepare for catch-up vaccination of children who could not receive IPV in the routine schedule.
Polio	SAGE requested WHO to complete the guidance on identification of potentially infectious materials (including stool and respiratory specimens) into 3 groups based on likelihood of being contaminated with VDPV2 or WPV2.	Oct 2016	Ongoing	The draft 'Guidance for completion of Phase I of GAPIII' has been circulated for comments.
Polio	SAGE advised GPEI to accelerate implementation of the WHO Global Action Plan for containment (GAP III) 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 17 Jan 2017, all 205 countries and territories have completed their reports on the first part of Phase I. 28 countries or territories have reported not retaining any OPV2/Sabin2 materials. The completion of this second part of Phase I will follow the publication of WHO's 'Guidance for the completion of Phase I of GAPIII', pending endorsement by the Containment Advisory Group (CAG). The release of mOPV2 in 6 countries for post-switch outbreak response further delays the completion of Phase I in these areas. Altogether, 30 countries reported the intention to retain PV2 materials (WPV2 or OPV2/Sabin2) in 78 designated poliovirus-essential facilities.
Polio	SAGE urged WHO to facilitate discussions and decision-making by National Immunization Technical Advisory Groups (NITAGs) to introduce IPV intradermal fractional dose use by providing necessary technical information.	Oct 2016	Ongoing	WHO prepared the communication and technical materials to NITAGs. The WHO secretariat is advocating the use of fIPV at both regional and country TAGs.
Polio	SAGE noted that the IPV supply situation is further deteriorating. Therefore, the programme should explore the possible use of devices facilitating intradermal administration (e.g. jet injectors, intradermal adapters).	Oct 2016	Ongoing	WHO is working on pre-qualification of both jet injectors and intradermal adapters. In addition, WHO is conducting several pilots of the use of these devices in immunization campaigns (e.g. Karachi, Pakistan).

Topic	Recommendations/Action Item	Meeting Date	Status	Comments and Follow up
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	<p>Inter-Cluster Transition Committees have been established in both WHO Regional Office for Africa (AFRO) and WHO Regional Office for the Eastern Mediterranean (EMRO). They are Chaired by the Directors Programme Management of the respective Regions. The Regional Offices are also members of the WHO Global Polio Transition Steering Committee established by the Director-generals Office. Headquarters (HQ) and Regional Colleagues are members of the Global HR Working Group that is planning for the effective and efficient reduction in the Polio Staffing levels in countries, regions and HQ.</p> <p>Guidance on Transition Planning, and Budget Rampdown figures for 2017 - 2019 have been provided to AFRO, EMRO and Regional Office for South-East Asia (SEARO), and the 16 polio priority transition countries by the Global Polio Eradication Initiative (GPEI) through the Transition Management Group (TMG). Financing has also been provided through the TMG to support Consultants, selected by the Regional Offices, who are assisting transition countries in conducting asset mapping, identifying country priorities and needs, and developing transition plans.</p> <p>Both AFRO and EMRO are also involved in the development of a Business case for Immunization in the African continent as a follow-up to the Addis Declaration on Immunization. Polio transition and its consequences will inform this business case.</p>
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 the Transition Management Group of the Global Polio Eradication Initiative is emphasizing the importance of this. All Transition Planning consultants are briefed/ trained on the Transition Guidelines.
Preferred Product Characteristics	SAGE noted the utility of Preferred Product Characteristics (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	<p>Malaria Vaccine Preferred Product Characteristics (PPCs) are finalized and available on WHO website: (http://apps.who.int/iris/bitstream/10665/149822/1/WHO_IVB_14-09_eng.pdf).</p> <p>Respiratory Syncytial Virus PPCs are now under development.</p> <p>In addition, 2 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/).</p> <p>The Zika vaccine TPP was updated through a 2nd public consultation, and is available on WHO website since 17 Feb: (http://www.who.int/immunization/research/development/zika/en/index2.html).</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>Regarding the Emergency Use Assessment and Listing (EUAL) procedure, the WHO Prequalification Team took note of SAGE recommendation and further development of the EUAL will consider relevant regulatory authorities including those of impacted countries.</p> <p>Further, a document entitled, "Vaccine evaluation in public health emergencies – review of regulatory pathways in selected countries" was prepared and presented to SAGE working group (WG) on Ebola vaccines in Aug 2015.</p> <p>In Oct 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 reviewed the document's progress in 2016. Evaluation of vaccines for public health emergencies was discussed in the 3rd meeting of the WHO Collaborating Centers Network on Vaccines in Seoul, in July 2016. Lessons learned from the Ebola crisis in West Africa and the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in Korea were discussed and several activities of the CC network were proposed. In addition, a new initiative called the Coalition for Epidemic Product Innovation (CEPI) was discussed as a framework in which a number of partners will work together to assure better preparedness for public health emergencies in future. The ECBS was also briefed about the CEPI in Oct 2016. In that context, further work on the development of regulatory standards has been undertaken and progress will be reported to the ECBS 2017.</p>

Topic	Recommendations/Action Item	Meeting Date	Status	Comments and Follow up
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 network of WHO Collaborating Centres (CC) on the Standardization of Vaccines has been established. At its 3rd meeting, the network agreed to establish a "Core Expert Group (CEG)" to assist the Expert Committee on Biological Standardization (ECBS) to review selected proposals for measurements standards. Proposals for replacement measurement standards are usually straightforward, with few strategic or scientific issues, and they would be the initial focus of the CEG. The ECBS agreed that the CEG could pre-review selected measurement standards in the vaccines area and thus help to streamline the ECBS review process. This process will be piloted in 2017.
Reports from other advisory committees on immunization	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	Since 2013, Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) includes 2 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 was issued in Q3-Q4/2016. The selection process is still ongoing with another call for nominations issued in Mar 2017, as further members will be rotating off in 2017.
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 WHO Prequalifications (PQ) team with regard to prequalification processes for both respiratory syncytial virus (RSV) vaccines and monoclonal antibodies (mAbs). The ECBS Guidelines for RSV vaccines are planned for development and possible adoption at Expert Committee on Biological Standardization (ECBS) 2018, as these are a prerequisite for consideration for PQ. The Essential Medicines and Health Products (EMP) department is considering an approach to PQ of mAbs. Intensive discussions continue about the most appropriate way to prepare for policy-making in Low and Middle Income Countries (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. 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)	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	Two country case studies (Zambia, presented to SAGE in April 2016, and Senegal) (WHO, JSI) and a global landscape analysis and literature review (UNICEF) have been conducted; learnings from this have been used to inform the draft global guidance on Establishing and strengthening a healthy child visit in the second year of life (2YL) for immunization and other health interventions. An advanced draft of the guidance document will be shared with and reviewed by the Immunization Practices Advisory Committee (IPAC) in Feb 2017. Country demonstration projects are also ongoing in Ghana and Malawi (CDC) and will continue to inform the global guidance.
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 Government for 10 000 doses have been put on hold until there will be a quality advice from the WHO Prequalification (PQ) team whether these vaccine would be acceptable. WHO is working on smallpox vaccine prequalification for the emergency stockpile. A WHO meeting took place in Geneva 7-8 Sep 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 Q1 2017.

Topic	Recommendations/Action Item	Meeting Date	Status	Comments and Follow up
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 will be held at 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.
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." These discussions are also well aligned with the fifth objective of the Global Vaccine Action Plan (GVAP), the Middle Income Country (MIC) Strategy endorsed by SAGE in April 2015, the 68th World Health Assembly (WHA) resolution on the GVAP in May 2015. WHO IVB Department, in collaboration with Essential medicines and health products (EMP) and with support from Linkbridge consulting funded by the Bill & Melinda Gates Foundation, is leading a Vaccine Shortage Project. The aim of the project is to act upon the recommendations and requests of SAGE and WHA by providing concrete proposals on WHO's role and actions to enhance information sharing for pre-empting and managing vaccine supply shortages. While all countries can benefit from this work, particular attention is paid to countries not supported by UNICEF Supply Division, PAHO, or Gavi. To ensure that any potential solution in this space builds on existing data, knowledge and processes, a first phase of the project, the Analysis of Assets, aimed to understand the extent of information available to WHO to be able to predict, pre-empt and act upon vaccine shortages. This includes both internal and external information. This phase also aimed to understand the extent of current project/mitigation work within WHO, vaccine by vaccine. This phase has been completed and a project report is available upon request. Based on the findings from Phase 1, Phase 2 of the project intends to develop concrete solutions to enhance WHO's ability to address vaccine shortages with a focus on filling current gaps in information sharing and supporting self-procuring countries. Using Bacillus Calmette-Guérin (BCG) to prototype to prototype solutions, an informed proposal on WHO's functions and operating model with regards to vaccine supply/demand/price data input, market analytics, output material and distribution will be developed. Draft Terms of Reference for the operating model -with related resource assumptions- will be made available by Q3 2017.

Topic	Recommendations/Action Item	Meeting Date	Status	Comments and Follow up
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	Since 2013, significant progress has been made to strengthen the Global IB-VPD and Rotavirus Surveillance Networks through recommendations from the 2013 global strategic review and annual meetings and consultations. By the end of 2016, we have made significant progress toward strengthening the Networks and meeting those goals. In 2016, the Global Rotavirus Surveillance Network comprised 101 sentinel surveillance sites in 48 countries and the Global IB-VPD Surveillance Network comprised 111 sentinel sites in 51 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 2016, 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). The surveillance platform has also been leveraged to monitor other VPDs, such as typhoid using the IB-VPD surveillance sites and other enteric pathogens such as norovirus, Shigella, and ETEC using the rotavirus network. 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 to monitor impact 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. We are discussing how to better integrate IB-VPD meningitis surveillance with existing meningococcal meningitis surveillance systems. We conducted a meeting in December 2016 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 and how to incorporate countries conducting surveillance outside of the Network. Finally, one of our main activities is to work with countries on making surveillance sustainable in the long term.

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 Universal Health Coverage composite indicator, and the Hepatitis B control strategy, three doses of Hep B vaccine). It was agreed to propose Global Vaccine Action Plan (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 Decade of Vaccine Working Group. In November 2016 at 4th meeting of the Inter-agency and Expert Group on Sustainable Development Goal Indicators (IAEG-SDG) accepted the new immunization indicator defined as 3.b.1 Proportion of the target population covered by all vaccines included in their national programme. WHO and UNICEF were identified as co-custodians for this indicator. The definition of the indicator and the proposed measurement needs to be developed and validated by SAGE Decade of Vaccine working group. A call is scheduled for May 2016 to further discuss potential options. The definition needs to be finalized or IAEG meeting scheduled for fall 2017 in order to include the indicator to 2018 SDG report.
-------------------------------	---	----------	---------	--

Topic	Recommendations/Action Item	Meeting Date	Status	Comments and Follow up
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. The most advanced vaccine candidates are GSK's M72/AS01E, the recombinant BCG VPM1002, M. VaccaeTM. M.vaccae is a heat killed homogenized lysate developed by Anhui Zhifei Longcom, China, which has been evaluated in Phase 3 for prevention of tuberculosis in healthy adults with latent TB infection, as well as as adjunctive immunotherapy with the aim to shorten TB treatment. Results have not been communicated. VPM 1002 is a recombinant BCG, originally developed by the Max Planck Institute; now licensed to the Serum Institute of India (SII) and being developed with Vakzine Projekt Management (VPM), Hannover, Germany. It is currently in Phase Ib/III trials, being compared to BCG in neonates in South Africa, as well as being tested for prevention of TB recurrence in adults in India. M72/AS01E a GSK adjuvanted protein vaccine candidate in phase Ib evaluation in Southern Africa, being tested for prevention of pulmonary TB, in previously infected adults. Primary results are awaited in the coming months. Secondary endpoints include safety and immunogenicity. 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. Upon PDVAC recommendation, WHO IVR is driving an effort to generate guidance on preferred product characteristics for TB vaccines targeted to adults and adolescents, with support from the Gates foundation.
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 (WG) on Typhoid Vaccines was established in Mar 2016 and the evidence review to support policy recommendations is ongoing. The Working Group will hold its face-to-face meeting 29-31 May. An ad hoc WHO meeting was scheduled for 3 Apr (including some SAGE WG members as well as non-SAGE WG experts) to review specific policy related issues and data to inform the SAGE WG process; a particular focus of the meeting will be to review the burden of disease in infants and young children and key considerations for optimum vaccination strategies using typhoid conjugate vaccines. Data on the safety of typhoid vaccines was reviewed by Global Advisory Committee on Vaccine Safety (GACVS) in Dec 2016. SAGE review of the draft recommendation form the SAGE WG is scheduled for Oct 2017. One licensed typhoid conjugate vaccine is undergoing WHO prequalification review.
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	Work is ongoing on the tool to assess "Missed Opportunities for Vaccination" (see item 284). On a broader level, a companion document to the Global Vaccine Action Plan (GVAP) focusing on Routine Immunization entitled "Global Routine Immunization Strategies and Practices" (GRISP) has been presented to the SAGE WG on DoV twice, and in Aug 2016 was published
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	Possibilities of using the SAGE framework in other public health areas and emergency settings are being explored.

Topic	Recommendations/Action Item	Meeting Date	Status	Comments and Follow up
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 Apr 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 20 June 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 took place on 10-11 Oct to develop consensus on the various guidance and priorities mentioned above and discuss how to best communicate and advocate for their implementation. Feedback from the meeting included that the envisaged operational manual missed important features while still being too long. Therefore the participants concluded that with having the revised and edited framework for decision-making along with the web-based tools, the operational manual was obsolete.</p> <p>The implementation guide and the framework for decision-making are currently with the editor. Further, a kick-off meeting took place with the software company to initiate the development of the web-based tools.</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	With the support from the Bill and Melinda Gates Foundation (BMGF), a point-of-care testing (POCT) prototype sample Oraquick collection device and POCT test system based on lateral flow and a reader combined with mobile phone, has been developed for the detection of measles specific antibodies in serum and oral fluid. The prototype showed high sensitivity and specificity (91 and 94% respectively for serum and 90 and 96% for OF). On top of that, measles virus genome could be reliably detected in the POCT strips and used for genotyping, even after prolonged storage for more than a month at 20-25°C. The added advantage was that the POCT was highly thermostable and the results showed high concordance with gold standard assay used in the Global Measles Rubella Laboratory Network (GMLRN). The assay is particularly useful in endemic settings as well as in settings near elimination of even post elimination and re-introduction. During a recent meeting of the Measles Rubella Initiative on Research and Innovation POCT came out as one of the top research priorities. It will allow monitoring disease using effective surveillance and evaluate programmatic efforts to ensure progress. It will also aid in developing and maintaining outbreak preparedness, and respond rapidly to outbreaks and manage cases. Field studies are now in phase 2 in different epidemiological and health care settings, including countries in different phases of measles control and with different health care infrastructures (Africa and South East Asia). Particularly the operational feasibility of using POCT/OF in a field setting needs to be determined. Currently, besides the measles Igm assay for oral fluid, capillary blood and serum, a POCT for rubella Igm is being developed. POCT for measles and tetanus IgG are being evaluated for the use on oral fluid and dried blood spots on filter paper.

Vaccine coverage	WHO to identify appropriate methods and develop guidelines for collecting, analysing, and interpreting biomarkers for validating coverage.	Nov 2011	Ongoing	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. 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. The data collection part of a pilot study has been conducted in Mongolia in 2016. Analysis of the survey results is underway. Based on the outcome, the working draft guidelines will be adjusted, amended and corrected where needed. The second pilot study is being planned to take place in Bhutan in February and is a joint seroprevalence study measles-rubella and hepatitis b and c. The final document is planned to be ready and published by end of 2017 and to be rolled out as a tool to evaluate the immune status of the target or targeted population.
------------------	--	----------	---------	---

Topic	Recommendations/Action Item	Meeting Date	Status	Comments and Follow up
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 quality, precision and usefulness of survey results and to reduce the cost of surveys, the Global Immunization Monitoring and Surveillance Group (GIMS) explored recent advances in sampling methodology; new technologies for constructing sampling frames, supervision of field work, data collection, and analysis; and alternative content, collection, analysis, presentation and linkages.</p> <p>An initial meeting was convened of the Department of Immunization Vaccines and Biologicals (IVB) Informal Advisory Group on Monitoring Immunization Programme Performance through Household and Community Surveys. The first meeting addressed the need to modify Demographic and Health Surveys (DHS) implemented by ICF International; and the UNICEF Multiple Indicator Cluster Surveys (MICS) and the WHO Immunization Cluster Survey to accommodate changes in immunization system strategies. In 2012, following a meeting with representatives of ICF and the MICS team, WHO and UNICEF provided written recommendation to these agencies to propose modifications to their standard recommendations on data collection, analysis and presentation of immunization coverage data.</p> <p>An informal working group was created to review and revise WHO guidance on measuring immunization coverage through household and community surveys. In 2013, the working group met 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 in 2014-2015. The proposed methods were reviewed in September 2014 by Immunization and Vaccines Related Implementation Research Advisory Committee (IVIR-AC). IVIR-AC agreed that the revised method for coverage surveys is the proper way forward, but that statistical expertise will be required to implement the survey in the field and provided other considerations, including the importance of using GPS technology, the need for qualitative studies and piloting of surveys in hard-to-reach settings. IVIR also noted that difficulties in monitoring progress and comparing cross-sectional data across methods and time must be addressed.</p> <p>Protocol for pilot testing was used in Bangladesh. In mid-2015, a working draft of the WHO Vaccination Coverage Survey Reference Manual was distributed and posted on the departmental website. Between 2015 and 2016, all or some aspects of the recommendations included in the new Survey Manual were used in Burkina Faso, Lao PDR, and to a lesser extent in Lebanon and for surveys following supplementary immunization activities (SIA) in Kenya, Swaziland, to name a few. Nigeria combined a MICS with a vaccination coverage survey and Pakistan planned its 2017 Vaccination Coverage Survey using the new Manual. In Dec 2015, a briefing workshop on the methodology for regional focal points and consultants was conducted. In 2016, countries in the African and Eastern Mediterranean regions were briefed. Between 2016 and early 2017, WHO in collaboration with UNICEF and CDC conducted trainings that brought together statisticians from developing countries (one Anglophone and one Francophone training), along with immunization program officers and consultants were conducted for countries from all regions, except EUR. A separate training was done in China for all provinces. It is expected that the WHO Vaccination Coverage Survey Reference Manual will be finalized in 2017, after experiences and lessons learned are shared and discussed. The revised recommendations will likely improve accuracy, by decreasing selection bias and reliance on maternal recall, and should also increase likelihood for adequate power, increase rigor and quality. The cost of the various trade-offs needs to be further explored.</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	<p>IVIR-AC reviewed methods, and encourages studies on vaccine delivery costing and financing (human papillomavirus (HPV), influenza and oral cholera vaccine (OCV)) and vaccine uptake/hesitancy.</p> <p>Non-specific effects (NSE) of vaccination and missed opportunities for vaccination sessions were on the IVIR-AC agenda in 2016 and 2017.</p> <p>Economic tools for influenza vaccines were presented at the June 2016 meeting. A malaria costing tool to help countries cost and plan RTS,S vaccine in their country will be reviewed at the Sep 2017 meeting.</p>

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	<p>A range of activities are now ongoing in this area. The in-depth tool, "A Guide to Tailoring Immunization Programmes (TIP)" is being used in at least 6 countries by WHO-EURO (European Regional Office), with at least 3 additional countries starting TIP projects in 2017, one of which in the Western Pacific Region. An evaluation of TIP implementation in the European Region from 2013-2016 was conducted in the second half of 2016. Findings will inform development of a new updated version of TIP in 2017.</p> <p>Additionally, the Univ. of Witwatersrand in South Africa has been contracted to adapt the TIP method for developing countries, with less intensive consultant-based inputs. This is being finalized and will be published in the first half of 2017.</p> <p>The Health Worker KAP tool has been completed and piloted with the assistance of JSI in Kenya. The final version will be published also in the first half of 2017.</p> <p>Lastly, in 2017 a range of new activities and materials are planned, with a focus on:</p> <ol style="list-style-type: none"> 1) promoting and scaling up use globally of the various tools and guidance developed by EURO on boosting acceptance and addressing hesitancy, 2) developing a range of tools targeted to health workers covering multiple injections, contraindications, and pain mitigation, and 3) a conversation guide informed by the latest evidence from the behavioural and social sciences. <p>Collaborations in this field are also being fostered with a number of experts and researchers from a diverse range of disciplinary backgrounds to informally help support WHO efforts in this area. Coordination with UNICEF, CDC, and other partners is also taking place to ensure alignment of efforts.</p>
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	<p>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.</p> <p>A Special Issue on Vaccine Hesitancy has been published in Aug 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 Aug 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 paper which outlines the results of the 2015 Joint Reporting Form (JRF) indicators on vaccine hesitancy and contains the matrix of determinants and the definition of vaccine hesitancy was published open access on 1 Mar 2017: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0172310.</p>
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	<p>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/</p> <p>The necessity to validate the research questions has been flagged to a newly established International Collaboration on Vaccine Acceptance.</p>

Topic	Recommendations/Action Item	Meeting Date	Status	Comments and Follow up
Yellow Fever	SAGE prioritized head to head non-inferiority studies of all 4 WHO prequalified Yellow Fever vaccines, as well non-inferiority studies in special populations. Of particular importance, given the consequences for international travel involving IHR requirements is the duration of protection with fractional dosing, including the potential need for revaccination. Safety and effectiveness assessments should be put in place when minimal effective doses are used.	Oct 2016	Ongoing	IVR has actively promoted the research agenda, and several relevant studies are in planning or execution phase. Fractional dose non-inferiority studies for all 4 prequalified vaccines will be conducted (funded, Africa), and long term immunogenicity will be assessed in a Brazilian cohort (funded). Immunogenicity study in DRC is on track.



World Immunization Week 2017, 24-30 April 2017

Theme: #VaccinesWork

World Immunization Week – celebrated in the last week of April – aims to promote the use of vaccines to protect people of all ages against disease. Immunization saves millions of lives and is widely recognized as one of the world’s most successful and cost-effective health interventions. Today, there are still 19.4 million unvaccinated and under-vaccinated children in the world.

Five years into the Decade of Vaccines

2017 marks the halfway point in the Global Vaccine Action Plan (GVAP) – endorsed by 194 Member States of the World Health Assembly in May 2012 – which aims to prevent millions of deaths from vaccine-preventable diseases by 2020 through universal access to immunization.

Despite improvements in individual countries and a strong global rate of new vaccine introduction, all of the targets for disease elimination—including measles, rubella, and maternal and neonatal tetanus—are behind schedule. In order for everyone, everywhere to survive and thrive, countries must make more concerted efforts to reach GVAP goals by 2020. Additionally, those countries that have achieved or made forward progress towards achieving the goals must work to sustain those efforts over time.

2017 Campaign Objectives

The main goal of the campaign is to raise awareness about the critical importance of full immunization throughout life, and its role in achieving the 2030 Sustainable Development Goals.

As part of the 2017 campaign, WHO and partners aim to:

- Highlight the importance of immunization as a top global health investment priority.
- Promote understanding of the action steps required to achieve the Global Vaccine Action Plan.
- Showcase immunization’s role in sustainable development and global health security.

Why immunization matters now more than ever

Expanding access to immunization is crucial to achieving the Sustainable Development Goals. Routine immunization is a building block of strong primary health care and universal health coverage—it provides a point of contact for health care at the beginning of life and offers every child the chance at a healthy life from the start.

Immunization is also a fundamental strategy in achieving other health priorities, from controlling viral hepatitis, to curbing antimicrobial resistance, to providing a platform for adolescent health and improving antenatal and newborn care.

Related links

[World Immunization Week 2017 campaign website: www.who.int/campaigns/immunization-week/2017/en/](http://www.who.int/campaigns/immunization-week/2017/en/)

[Global Vaccine Action Plan 2011–2020: www.who.int/immunization/global_vaccine_action_plan](http://www.who.int/immunization/global_vaccine_action_plan)

[Global Vaccine Action Plan](http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_34-en.pdf?ua=1) – Report by the Secretariat to the World Health Assembly in May 2017: http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_34-en.pdf?ua=1

[WHO's work on immunization: www.who.int/immunization](http://www.who.int/immunization)

**REPORT OF THE
REGIONAL IMMUNIZATION TECHNICAL ADVISORY GROUP MEETING**



TABLE OF CONTENTS

TABLE OF CONTENTS	I
ACRONYMS	II
EXECUTIVE SUMMARY	III
1.0 BACKGROUND	1
2.0 OPENING CEREMONIES	2
3.0 TECHNICAL SESSIONS	5
3.1 OVERVIEW	5
3.2 INFORMATION	6
Update on Status of implementation of RITAG Recommendations	6
Progress Report on Immunization Coverage in the WHO African Region.....	7
Improving Immunization Coverage through Equity Lens.....	9
Addis Declaration on Immunization – Roadmap Development	10
3.3 FOR DISCUSSION AND DECISION.....	12
3.3.1 MEASLES/RUBELLA ELIMINATION STRATEGIES FOR THE WHO AFRICAN REGION	12
Challenges in Attaining Measles/Rubella Elimination Targets	12
Report of the External Evaluation of the Measles Elimination Strategy 2011-2020 in the African Region	14
3.3.2 POLIO ERADICATION AND ENDGAME STRATEGY	16
Global Polio Updates – Including IPV Vaccine Supply and Transition Overview	16
Polio Update in Africa – focusing on the lake Chad Basin Region and other risks	18
GPEI Ramp-Down and Transition Planning in the African Region – UNICEF & WHO Perspective	19
Global Strategy for Eliminating Yellow Fever Epidemics	21
Challenges in Eliminating Yellow Fever Epidemics in Africa.....	22
3.3.4 MATERNAL AND NEONATAL TETANUS ELIMINATION IN AFRICA	23
Progress towards MNT Elimination in Africa	23

ACRONYMS

ADI	Addis Ababa Declaration on Immunization in Africa	LMIC	Low and middle income countries
AFRO	African Regional Office	LQA	Lot Quality Assurance
AFP	Acute flaccid paralysis	MCIA	Ministerial Conference on Immunization in Africa
AGE	Acute Gastroenteritis	MCH	Maternal and Child Health
ANC	Ante-natal care	MCV	Measles-containing vaccine
AVAREF	African Vaccine Regulatory Forum	MCV1	First dose of MCV
BMGF	Bill and Melinda Gates Foundation	MCV2	Second dose of MCV
bOPV	Bivalent oral polio vaccine	MNT	maternal and neonatal tetanus
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	MOV	Missed Opportunity for Vaccination
CSO	Civil society organizations	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 Organization
EYE	Elimination of Yellow Fever Epidemics	PCR	Polymerase Chain Reaction
FRH	Family and Reproductive Health	PCV	Pneumococcal conjugate vaccine
Gavi	Global Alliance for Vaccines & Immunization	PID	Pneumococcal invasive disease
GIS	Geographic Information systems	RCV	Rubella-containing vaccine
GPEI	Global Polio Eradication Initiative	RED	Reaching Every District Approach
GPS	Geospatial positioning system	RITAG	Regional Immunization Technical Advisory Group
GVAP	Global Vaccine Action Plan	RV	Rotavirus Vaccine
HPV	Human Papilloma Virus Vaccine	SAGE	Strategic Advisory Group of Experts on immunization
HR	High Risk	SIAs	Supplementary Immunization Activities
HSS	Health systems strengthening	tOPV	Trivalent oral polio vaccine
ICC	Inter-Agency Coordinating Committee	RITAG	Task force for Immunization
IDSR	Integrated Disease Surveillance & Response	TBA	Traditional Birth Attendants
IMCI	Integrated Management of Childhood Illness	TT	Tetanus toxoid
JRF	The WHO UNICEF Joint Reporting Form	VCMs	Volunteer community mobilizers
UNICEF	United Nations Children's Fund	VHF	Viral Hemorrhagic Fevers
LGA	Local Government Area	VPD	Vaccine Preventable Disease
		YF	Yellow Fever
		WHA	World Health Assembly
		WHO	World Health Organization
		WPV	Wild poliovirus

EXECUTIVE SUMMARY

The Regional Immunization Technical Advisory Group (RITAG) met in Dakar, Senegal at the *Radisson Blu* Hotel from 12th to 13th December 2016 for its second ordinary meeting of the year. Dr Deo Nshimirimana, the WR Senegal welcomed the participants on behalf of the Regional Director, Dr Matshidiso Moeti and the meeting was officially opened by the Minister of Health and Social Development, Senegal. Present at the opening and subsequent sessions were immunization partners and donors as well as representatives of civil society organizations, immunization staff from the countries and various levels of WHO (ISTs, Regional Office and Immunization and Polio Directors from HQ).

The primary goals of the meeting were to update the RITAG members on progress made in the programme, current priorities as well as levels of achievement of the recommendations from the previous RITAG meetings and to seek their advice and guidance on current specific challenges. Some of the recent priority areas in immunization in the African Region were discussed in sessions of the meeting after the brief presentations made by the secretariat. 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:

1. RITAG RECOMMENDATIONS ON SUSTAINABLE IMMUNISATION PROGRAMMES AGAINST THE BACKDROP OF POLIO TRANSITION AND GAVI GRADUATION

1.1. Ensuring Alignment of Strategic Documents

RITAG notes with satisfaction the development of the roadmap to evaluate the Addis Ababa Declaration on Immunization in Africa (ADI). The RITAG notes also that there are now a number of strategic documents directing progress in immunization in the region for the next 5-10 years. To ensure coherence between new strategic documents pertaining to regional and national immunization programmes, it is important that each newly developed plan, roadmap, monitoring and evaluation framework be related to the Global Vaccine Action Plan (GVAP) and the Regional Strategic Plan on Immunization. This should include reference to human rights and rights of the child, national ownership and accountability, community demand and the integration of immunization services in a strengthened health system.

RITAG recommends that

- The drafted ADI roadmap is framed in this manner and is reviewed by the RITAG members before its finalization.

1.2. Polio Transition Planning

RITAG notes with concerns that there appears to have been insufficient coordinated planning for polio transition and also notes that in many countries polio resources are being used for services beyond polio eradication activities. Acknowledging that polio transition is inevitable and is imminent, urgent attention to better planning is required to avoid adverse impact on immunization, surveillance and emergency response programmes. RITAG also supports the work WHO/AFRO has embarked on to develop a WHO business case for immunization for the African Continent and has taken note that this business case will aim to ensure sufficient commitment of resources for WHO to continue to support Member States on the African continent achieve the GVAP targets as the Global Polio Eradication Initiative (GPEI) ramps-down and closes and Gavi support phases out over the coming years as countries on the African continent transition out of Gavi support.

RITAG recommends that:

- A detailed programmatic risk analysis (assessment & mitigation) be conducted on the projected impact of the GPEI ramp-down and closure and Gavi transitioning, on immunization programmes & disease surveillance systems in the African region. Gavi & other development partners to consider commissioning this study.
- An independent assessment of countries' requirements post-polio transition be supported by donor partners. This should include a human resource development and redeployment plan.

1.3. Immunization Coverage

The RITAG is deeply concerned by the stagnation of the regional immunization coverage over the past 5-7 years, the persistently very low coverage in a small number of countries, the more recent decline in coverage in other countries and the growing threat that emergencies pose to immunization coverage.

The RITAG recommends that:

- In the next 12 months, WHO/AFRO undertakes an in-depth country or sub national studies to determine reasons for this stagnation, understand key drivers of immunization coverage trends, inform strategies with measurable indicators and time frames for member states to improve on their immunization coverage.
- WHO/AFRO and UNICEF work with countries to develop strategies to strengthen meaningful participation of communities, civil society organizations and the private sector in promoting routine immunization.
- WHO/AFRO and UNICEF compile and share best practices in community based and led surveillance and monitoring including use of community registers, for use by district and frontline health staff.
- WHO/AFRO and UNICEF provide guidance for district and frontline health staff to foster community planning and action to promote immunization as part of community delivery of child and family health services.

2. RITAG RECOMMENDATIONS ON YELLOW FEVER

2.1. Implementing the Elimination of Yellow Fever Epidemics (EYE) Strategy

The RITAG recognizes that while it is not possible to eradicate yellow fever, elimination of epidemics is feasible and is essential against the backdrop of global warming, the changing distribution of *Aedes aegypti*, migration and urbanization. The RITAG notes the recent successful curtailment of yellow fever outbreaks in Angola and DRC and the prevention of outbreaks developing in Kenya and China following exportation from Angola. The RITAG appreciates the efforts of the countries supported by WHO, UNICEF and partners in achieving this goal. RITAG strongly endorses the newly developed WHO strategy for the Elimination of Yellow Fever Epidemics (EYE) strategy. The RITAG supports the development of the Regional Implementation Framework currently in progress and notes that a proposed Preventive Campaign Schedule for at risk countries that WHO AFRO is developing as part of this framework.

RITAG recommends:

- Countries that have undertaken risk assessments should implement actions outlined in the EYE strategy appropriate for their level of risk. This is particularly urgent for countries at high risk. For countries that have not yet undertaken risk assessment this should be urgently conducted with support of WHO, UNICEF and partners.
- The regional implementation framework and responses must include community involvement strategies for Yellow Fever surveillance, outbreak response and prevention.
- The proposed preventive campaign schedule should be based on country's risk assessment and projected needs and should be endorsed by countries and the vaccine stock required to support the schedule should be evaluated.
- The Regional Implementation Framework should be reviewed by RITAG in January 2017 and presented to the Regional Programme Sub Committee (PSC) in April, 2017.
- WHO AFRO should aim to present the draft Preventive Campaign Schedule to RITAG for review at the June 2017 RITAG meeting.

2.2. Strengthening Yellow Fever Coverage as Part of Routine Immunization

The RITAG notes that the low routine immunization coverage of Yellow Fever vaccines contributed to the recent Yellow Fever outbreaks and poses a significant risk for future epidemics. Despite adequate supplies of yellow fever vaccine for routine immunization programmes being available, of the 34 at-risk countries, 12 countries have low immunization coverage (<70%), six countries have moderate coverage (70-80%) and there is no yellow fever vaccine in routine immunization in 11 at risk countries. This situation will lead to a growing

cohort of unvaccinated children. As yellow fever vaccines are offered on the same schedule as measles vaccine, it is unclear why coverage is lower than measles in some countries.

RITAG recommends:

- In the context of routine immunization, WHO/AFRO should work with countries to implement a research agenda exploring why yellow fever immunization does not meet targets. Resulting data should be used to develop national strategies to address identified obstacles.
- WHO/AFRO and UNICEF should work with high-risk countries without yellow fever vaccines in their EPI programs to introduce the vaccine.

2.3. Yellow Fever Fractional Dosing Strategies

Currently SAGE recommends that fractional dosing of Yellow Fever vaccines can be used in outbreak settings when vaccine supplies are limited. This recommendation is based on limited clinical trial data that suggests that fractional dosing is a safe and effective strategy. In the recent Yellow Fever outbreak in Kinshasa, the limited yellow fever vaccine stockpile and the size of the population requiring immunization (around 10 million people) necessitated the use of a fractional dosing strategy. At the time, the plan was to re-immunize those who had received a fractional dose with a full dose after one year. However, there is now an ongoing study in Kinshasa to evaluate the safety and immunogenicity of fractional dosing up to one year post vaccination and the results will be available later in 2017.

RITAG recommends:

- Once the clinical trial data are available in 2017, that the data are urgently submitted as a peer review publication and that SAGE reviews the data and makes further recommendations on the need or otherwise for a repeat full dose of Yellow Fever vaccine following fractional dosing.
- WHO/AFRO develops a communication strategy for the Democratic Republic of Congo (DRC) government and to the community, addressing why the implementation of a full dose of yellow fever vaccine at one year may be delayed or may not be required.
- Noting the exportation of yellow fever virus from Angola to China and Kenya during the recent outbreak, the IHR 2005 requirement for the use of a full dose of Yellow Fever vaccine with supporting certification must be enforced. The EYE strategy recommendation of double-checking travelers upon entering into or arriving from an at-risk country must be enforced. Travelers, who had previously received only the fractional dose of the Yellow Fever vaccine during the campaigns, must receive the full dose of Yellow Fever vaccine before travelling. All countries must enforce and monitor implementation of IHR requirements on Yellow Fever.

- WHO/AFRO sensitizes regional NRAs on the use of fractional dosing and the SAGE and RITAG recommendations

2.4. Yellow Fever Vector Control

In the July 2016 RITAG meeting, RITAG recommended that lessons on vector control in Brazil should be shared with Angola and this was done. However, it remains unclear whether vector control strategies across the region are being driven by potentially duplicative pathogen specific programmes (e.g. Dengue, malaria) rather than being integrated.

RITAG recommends:

- WHO AFRO should review all current vector control programmes and produce guidance for entomological monitoring and integrated vector management, taking into account existing vector control activities. Viral amplification in vectors should be introduced into selected regional laboratories to strengthen surveillance and improve prediction of yellow fever outbreaks.
- If not already in progress, WHO Geneva should consider the development of a rapid diagnostic test for yellow fever.

3. RITAG RECOMMENDATIONS ON POLIO

3.1. Intensifying Polio Eradication Efforts.

The Nigerian experience showed that in inaccessible areas where surveillance and vaccination activities were not conducted due to insecurity, it is possible for wild poliovirus to circulate undetected for 4-5 years. Due to the many population movements in the region (migrant populations, nomadic, traders, internally displaced persons and refugees), there is an increased risk of polio circulation beyond Nigeria and into the Lake Chad region, Central African Republic (CAR) and beyond. In addition, because of low immunization coverage in the region, wild poliovirus and circulation vaccine derived poliovirus (cVDPV) cases have occurred in otherwise stable countries such as Chad, Angola and Madagascar.

RITAG recommends:

- WHO AFRO should work with countries with inaccessible areas and/or low routine immunisation coverage, to undertake the risk assessments and implement initiatives to strengthen surveillance and vaccination activities by first quarter of 2017.
- Due to the risk of importation of polioviruses from countries with continued transmission, WHO should assist countries to intensify activities to strengthen active and passive surveillance, including use of Geographical Information System (GIS) technologies to provide evidence that these activities are being carried out. Evidence of improvement in surveillance should be presented to the July 2017 RITAG meeting.

- WHO AFRO should support countries to increase vaccination of targeted children by mapping migratory routes and intensifying transit vaccination and synchronized cross-border activities.

3.2. Accelerating Laboratory Containment

The RITAG notes with concern the reluctance by some countries to finalize the documentation of phase 1b laboratory containment with destruction of polioviruses and potential poliovirus infectious materials. RITAG regards this non-compliance as a threat to the timely completion of the eradication schedule and a risk for re-introduction of polioviruses.

RITAG recommends:

- WHO AFRO continues to support countries to complete this process and that RITAG members use their local and regional contacts to advocate for the completion of laboratory containment activities

3.3. Ensuring IPV Supply for Risk Countries

The RITAG was informed that because of the globally deteriorating Inactivated Polio Vaccine (IPV) supply situation, the GPEI programme is no longer in a position to ensure that all countries in the tier 2 category of risk continue to receive uninterrupted supplies of IPV. The SAGE has recommended that all infants in tier 1 and 2 countries receive some IPV vaccine and that fractional intradermal dosing is acceptable in these settings.

RITAG recommends:

- All tier 2 countries in the African region should adopt a fractional injectable device (ID) dose strategy to ensure maximum possible coverage with the limited quantities of IPV available. This can be done with a two ID fractional dose schedule administered at 6 weeks and 14 weeks starting as soon as possible in 2017. An alternative would be for the country to postpone IPV vaccination to 2018 and then conduct a campaign using one fractional dose IPV to prime the cohort of children not vaccinated with IPV.
- WHO AFRO requests Gavi to consider support the introduction of the IPV fractional dose schedule through the provision of ID syringes and ID adapters and grants for changing vaccine presentations.
- The GPEI programme should explore support for SIAs for countries that are not Gavi eligible.

4. RITAG RECOMMENDATIONS ON MNTE

4.1. Creating Strategies and an Investment Case to complete MNTE

The RITAG notes that the AFRO region has committed to a maternal and neonatal tetanus (MNT) elimination target by 2020 but 7 countries have yet to achieve elimination and there is a global funding shortfall. RITAG also noted that as MNT occurs in the poorest communities including those that are hard to reach, MNT should be regarded as an indicator of inequity in the context of the SDGs. In addition, recent cases of tetanus resulting from male circumcision in older boys/men have revealed an immunity gap requiring strengthened routine immunization for girls and boys. RITAG also noted that MNT elimination has been most effectively achieved in settings where immunization and pregnancy interventions are integrated and there is a comprehensive approach to implement MNT elimination measures. RITAG recognizes that a comprehensive strengthened surveillance strategy for countries post elimination and those yet to eliminate is required.

RITAG recommends:

- WHO HQ to fast track the development of the MNT elimination investment case and resource mobilization strategy, within the context of equity and health systems strengthening, to secure predictable and timely funding to support countries to achieve and maintain MNT elimination.
- WHO AFRO to develop a detailed, practical and budgeted Regional plan (2017 – 2020) for resource mobilization and focused programme implementation to achieve and maintain MNT elimination in the Region by 2020.
- Countries to utilize all possible opportunities including Gavi HSS funding and GPEI resources to assure that MNT surveillance is conducted and data are used for program action.
- Noting that in some countries a siloed approach to programmatic funding (e.g. through EPI or MCH) is affecting optimal delivery of MNT elimination interventions, WHO AFRO and UNICEF to support countries to develop national plans for the achievement and maintenance of MNT elimination with clear roles for the national immunization and reproductive health programmes, and appropriate channeling of funding flows.
- WHO and partners to identify a champion / ambassador for the MNT elimination program to help scale up advocacy efforts and mobilize resources.
- WHO AFRO to explore the possibility of renewing MOH commitments for MNT elimination at the highest level, possibly by tabling the issue at the Regional Committee Meeting.
- WHO AFRO to work with partners to support a new post in AFRO with a full-time focus on MNT elimination programmes and broader tetanus issues.

- WHO and UNICEF HQ to scale up efforts to work with the vaccine manufacturers to support the manufacture and supply of TT in Uniject to widen programmatic opportunities in remote and hard to reach populations.
- Noting Gavi's prioritization of equity, Gavi to consider including Td in its 2017 VIS review and to also review HSS funding for countries who have yet to eliminate MNT and those who have recently achieved elimination.
- WHO and UNICEF to support countries to:
 - Review and adjust their routine immunization schedules to ensure tetanus protection over the life course and in both sexes noting that this will reinforce the importance of both the second year of life platform and a pre-adolescent or adolescent platform linked to HPV vaccination. The schedule should include 3 priming doses in infancy and 3 booster doses in childhood/ adolescence to be given preferably during the 2nd year of life, at age 4 – 7 years, and at age 9 – 15 years and ensure that doses received are documented.
 - Shift from TT to Td formulation as the preferred option for children ≥ 4 years.
- WHO and UNICEF to support countries to utilize the existing Integrated Disease Surveillance Strategy, to improve the quality of monitoring, case investigation, and reporting of tetanus cases to improve programme performance.
- For countries that have achieved elimination, WHO and UNICEF to support countries to undertake annual data reviews of maternal and child health and EPI district performance, and identify and intervene in districts at high risk of an increase in MNT cases, where feasible, serosurveys should be used to validate assessment of identified risk.
- MNT risk assessment is used together with UNICEF's equity assessment exercise to frame MNT elimination strongly as an equity issue, and implement corrective programmatic actions.
- As elimination comes nearer and the AFRO region poses a risk to achieving this goal, that RITAG receives reports on progress to polio eradication every year.

5. RITAG RECOMMENDATIONS ON MEASLES ELIMINATION AND RUBELLA CONTROL

5.1. Accelerating Measles Elimination Efforts and Rubella Vaccine Introduction

The RITAG notes that the AFRO region has committed to a 2020 target for measles elimination. The RITAG is concerned about the current uneven progress and challenges for measles elimination with the majority of countries in the region failing to reach 90% coverage for first dose of measles containing vaccine (MCV1) and with much lower coverage for second dose of measles containing vaccine (MCV2). RITAG also notes that to date only 17 AFRO countries have introduced rubella vaccine and while more countries have applied for Gavi funding to introduce rubella vaccines, it remains premature for the region to consider a rubella elimination

target at this time. However, RITAG notes that while rubella and Congenital Rubella Syndrome (CRS) surveillance is very weak, there is currently a CRS surveillance study being undertaken in 7 countries in the region, and the data being generated will be used to advocate for rubella introduction. The RITAG regards the success of measles immunization programmes as a sensitive indicator of effective routine immunization systems and of an effectively functioning health system. The RITAG recognizes that there is no appetite among donors to commit to a vertically driven measles eradication programme similar to polio, but believes that attainment of measles elimination in the region would be a strong indicator of strengthened routine immunization programmes and effective health systems. The RITAG is also concerned that the withdrawal of polio eradication funding could further weaken routine immunization systems and progress towards measles elimination if not properly managed. While the region is not nearing elimination yet, there is merit in establishing a Regional Verification Commission, as this could provide guidance, oversight and advocacy in support of the elimination efforts in the region. The RITAG greatly appreciates and provisionally endorses the Mid-Term Review of the Measles Programme subject to incorporation of inputs from the RITAG members.

RITAG recommends:

- RITAG members provide inputs on the Mid-Term Review by 20 December 2016, to allow the external mid-term review team to finalize and submit the report by the 29th December 2016.
- WHO AFRO should:
 - Develop a budgeted action plan for the implementation of the recommendations of the Mid-Term Review for both WHO AFRO and for countries.
 - Support countries to develop plans for the implementation of these recommendations with a focus on laboratory support and surveillance. Those plans should be integrated in the country annual and multi-year plan for immunization. Gavi eligible countries should be encouraged to use HSS funding to support surveillance and laboratory activities.
 - Develop a monitoring and evaluation plan consistent with GVAP, the Regional Strategy and the ADI.
- WHO AFRO to work with countries to expand the CRS Sentinel surveillance network in the Region, use available data for wider advocacy, and to promote the introduction of rubella vaccines by Member States.
- WHO AFRO to establish a Regional Verification Commission for measles elimination and for the 7 countries nearing elimination, WHO AFRO should assist countries in setting up national verification committees tasked with the responsibility of compiling evidence, and supporting advocacy for measles elimination.

1.0 BACKGROUND

This is the second of the two regular meetings of the Regional Technical Advisory Group (RITAG) on immunization in the African Region in 2016. The goal of this meeting was to appraise the performance of the immunization programme since the last meeting in June 2016. Consequently, the implementation of the action points from the last meeting were scheduled to be reviewed along with the review of other programme implementation performances. The level of progress and challenges were also marked for review with suggestions given for remedial actions where necessary.

Specifically, the meeting was called to, among other things; apprise RITAG members on level of successes in implementation of the recommendations from the last meeting. The broad topics discussed include polio eradication in the African Region and planning for polio legacies post eradication as well as measles rubella elimination strategies for the African Region. Others are elimination of Yellow Fever Epidemic (EYE) and maternal and neo-natal tetanus (MNT). There were also issues presented to the RITAG as information, namely update on status of implementation of RITAG Recommendations, progress report on immunization coverage and equity in the WHO African Region as well as improving immunization coverage through the equity lens and Addis declaration on immunization – Roadmap development.

The report presented here presents a detailed account of the meeting and its key achievements.

2.0 OPENING CEREMONIES

The WHO Representative for Senegal, Dr Deo Nshimirimana, welcomed participants to Dakar, Senegal for the RITAG meeting. He thanked the Senegalese authorities and in particular the Minister of Health and Social Development for her consistent readiness to accommodate WHO meetings, and to support the regional and world activities by WHO and other partners. He also thanked the Regional Director WHO in the African Region, Dr. Moeti Matshidiso for authorizing the hosting of this important meeting in Dakar.

The RITAG serves as an independent advisory group of the WHO Regional office for Africa charged to provide strategic recommendation in the field of vaccines and immunization. It gives advices and recommendations to the Regional Director in relation to the policies and strategies on immunization, research and development of the vaccines and technology, among others. Dr Nshimirimana noted also that the mandate of the RITAG is not limited to the immunization of the children, but relates to all the diseases with vaccine prevention and all the age groups.



The opening ceremony of RITAG December 2016

In the past immunization programmes focused on the infants and a limited number of traditional vaccines. Today, the world of immunization has evolved. We now have the development and the availability of many new vaccines targeting various age groups, the emergence of new technologies, the increase in the vigilance of the public for the questions of vaccine security, the reinforcement of the procedures of regulation and approval of the vaccines, the need to widen the vaccine calendar by taking account of all the age groups and the populations at risk are as many subjects which claim a very detailed attention. The key of the improvement of immunization systems and the sustainable introduction of new vaccines and technologies of vaccination is, for the countries, to make sure that they have the evidence necessary and have transparent procedures which allow a decision making. He called for the prioritization of immunization programme, the development of new strategies and in the introduction of the new vaccines and technologies.

He further noted that the recommendations that will result from the 2 day meeting of the RITAG will be used for directing the actions of the countries in reinforcing immunization activities and monitoring of the diseases for the reduction of the morbidity and mortality of children < 5 years and thus accelerating the realization of the Sustainable Development Goals (SDG). He ended by wishing the participants fruitful deliberation.

Professor Helen Rees, the Chair of the RITAG also thanked the Minister for gracing the occasion with her presence despite the public holidays. She lauded the minister for her career as a distinguished scholar and administrator. All the same, she noted that coming into the room this morning, she was struck by the extra-ordinary energy in the room and the presence of men and women poised for work.

Professor Rees also acknowledged the RITAG members and also expressed her excitement about what the committee will do in strengthening immunization. She noted that if the group can mobilize the communities and gets the people to embrace immunization and demand immunization services it would have strengthened immunization, especially as it concerns equity.

On his part, Dr Richard Mihigo, the Immunization and Vaccine Development (IVD) Programme Coordinator thanked the WR for the kind words and encouragement. He reiterated the gratitude of the AFRO leadership for his hosting the RITAG. He also thanked the minister profusely for making time to be with the group and declare the meeting open. He then took the Minister and the participants through the programme of work for the two days before inviting her to officially declare the meeting open.

Declaring the meeting open, the Minister of Health and Social Development in Senegal noted that it was a great pleasure for her to be present in the house. She expressed her delight in seeing some familiar people in the audience and also given the great honour to declare the meeting open. She thanked WHO and its partners for the decision to hold the meeting in Senegal. She welcomed all the participants on behalf of the President and encouraged participants to make themselves at home.

Before formally declaring the meeting open, she took opportunity of her recognition to reiterate her gratitude to the immunization group for the onerous tasks they have engaged in. She noted the contributions of UNICEF and Gavi and other great immunization partners. She emphasized that immunization is pivotal in health because of its ability to prevent diseases and save lives. She also stressed that the originality of the RITAG meeting stems from its focus on matters that are not only topical but engage the international community especially the Sustainable Development Goals (SDG).

She noted that Senegal, like other countries subscribe to this initiative. According to her, immunization saves life and prevents morbidity and mortality. She stressed that a lot of progress has been made in the introduction of new vaccines and improvement in coverage. She mentioned that her country is exploring other options to increase access and enhance equity. She encouraged the RITAG to look into the issues of Human Papilloma Virus (HPV) because the women are suffering from cervical cancer. She called on the RITAG to look at infant mortalities, polio and measles. She noted that in Senegal there is a re-emergence of measles.

She also enjoined members to consider issues of sustainability. She noted that there are obstacles that must be overcome to promote equity and increased coverage. Some of these challenges include availability and affordability of vaccines. She advised that while Gavi is negotiating with UNICEF, the immunization programmes in the Region should begin to consider the situation of countries graduating from Gavi support. She encouraged the AFRIVAC initiative to help with cost of vaccines. According to her, AFRIVAC will help mobilize resources for vaccine but there is still need to think of other innovative options for vaccine financing.

Given the attraction of the topics, she regretted that she will not be able to sit through the sessions and listen to the practical hands-on recommendations. She however assured the RITAG of her support and resolved to examine the recommendations that will emanate from the meeting to improve immunization. On this note she declared the meeting open and again thanked the RITAG for the choice of Senegal for this meeting.

3.0 TECHNICAL SESSIONS

3.1 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 populations of Africa, and indeed the world, against vaccine preventable diseases; discuss challenges and seek expert orientation, from the RITAG members, on how to better deliver on WHO mandate to the people of the region and the world. Of particular interest were broad issues like polio eradication in the African Region and planning for polio legacies post eradication as well as measles rubella elimination strategies for the African Region. Others are elimination of Yellow Fever and maternal and neo-natal tetanus. There were also issues presented to the RITAG as information, namely update on status of implementation of RITAG Recommendations, progress report on immunization coverage and equity in the WHO African Region as well as improving immunization coverage through the equity lens and Addis declaration on immunization – Roadmap



During a technical session in the RITAG 12-13 December, 2016.

A total of 12 technical presentations were made. Three of these were for information while nine were made for RITAG decision and recommendations. The presentations provided participants with the necessary background information on the status of immunization and key vaccine preventable diseases (VPDs) in the African Region. The presentations were followed by discussions leading to actionable recommendations. The presentations, highlights of subsequent discussions and the recommendations are summarized below.

3.2 Information

Update on Status of implementation of RITAG Recommendations

Dr Masresha Balcha, WHO/AFRO

There were 28 action points from the June 2016 RITAG meeting. Of these two were fully achieved. Another 2 were not achieved while 24 others were in progress because activities addressing these recommendations are continuous. The presenter then proceeded to details of actions taken to implement the recommendations in the areas of immunization coverage and equity; polio eradication; vaccine regulation and universal health coverage. Others recommendations were related to measles and meningitis elimination.

Comments and observation

RITAG members noted that the steps taken in the implementation of the recommendation were not clear and the term ‘in progress’ seem too fluid. For instance they wondered what steps will be taken for the mobilization of resources. This should be linked to the Regional strategy. They also expressed concern about the issues of data quality which seem to be persistent and are not going to go away. RITAG Members demanded to see steps taken by the organization to support countries to improve data quality.

They also emphasized on some of the emerging issues on human resources from polio eradication initiative. Thus members wondered how RITAG can capture some of the points made to reach the remaining targeted persons, given the polio transition.

On non-implementation of the Brazzaville initiative due to lack of funding, the Director of Polio programme in WHO/HQ explained that there has been delay in funding due to administrative issues. He however stressed that the funds are there and warned that we cannot afford the delay because surveillance is critical

Action Points	Status	Comments
Countries, especially those reporting high immunization coverage, should triangulate available data to improve the accuracy of population immunity estimates.	In progress	Developed the Regional data quality strategy <ul style="list-style-type: none"> Development of countries strategic and annual data quality improvement plans following a system and DQR with clear monitoring and evaluation mechanisms Establishment of national Data Quality teams in countries (EPI, HIS, National statistics offices, partners...) Integration of immunization program requirements into integrated HIS such as DHIS2 platform Support countries in this process (16 countries already trained)
WHO AFRO to expand research agenda to include the development of new diagnostic tools, mapping, population denominator estimates, and innovative vaccine delivery strategies.	In progress	<i>Strategic framework for research and development in immunization is underway. Prioritization of research agenda being done.</i>

Figure 1: Status of implementation of some action points from last RITAG June 2016

Progress Report on Immunization Coverage in the WHO African Region

Dr Richard Mihigo, WHO/AFRO

The presenter opened the presentation by noting that though immunization has recorded significant improvement since 1988 it has however stagnated in the last five years. He noted for instance that polio eradication had come a long way. The recent cases in Nigeria however are a wake-up call and warning that we are not yet there. The same is the case with measles. He lamented that the Region is off track on most of the GVAP targets. A number of factors have had negative impacts on the immunization coverage. Examples are Ebola Outbreak, YF outbreak, security challenges, etc.

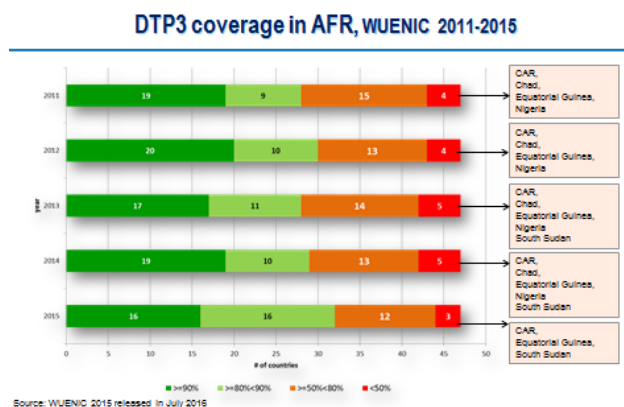


Figure 2: Trend in Immunization Coverage

He presented data showing that 1/3 of the countries have had improved coverage but majority of the countries are not making enough progress. Only 7 countries have so far maintained coverage of >80% in all districts. There are huge gaps especially in terms of equity. He stressed that nothing has changed in terms of unvaccinated children, despite the slight decrease in number of unvaccinated children in the Region.

One area where the Region has made progress is in the introduction of new vaccines. Network has been established in 31 countries on Rota surveillance. There is evidence of positive impact of new vaccine introduction, Acute Gastroenteritis (AGE) admission fell by almost 50% after the introduction of Rota in Rwanda for instance. Similar data for pneumococcal vaccine do also exist.

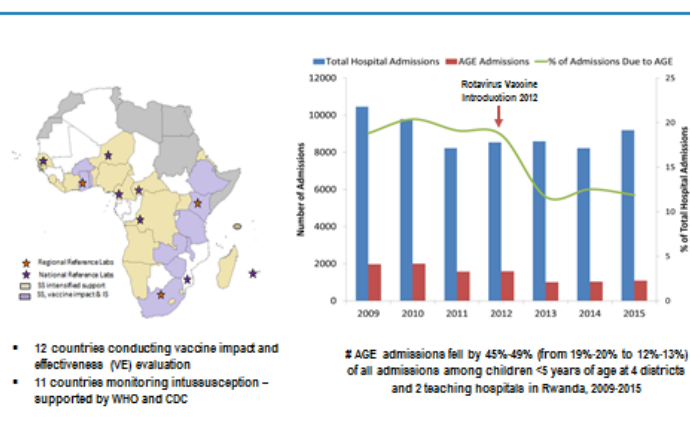


Figure 3: Evidence of new vaccine introduction impact

On data quality, the presenter noted that the secretariat will take steps to focus on the recommendation of RITAG in that regard. He stressed that the WHO/AFRO Secretariat is working closely with WHO/HQ in this respect. He reported that the WHO/AFRO has put together a Regional Data Quality Group in collaboration with WHO/HQ. He also reported that

the Region is working closely with other immunization partners to support countries in improving data quality. In his words, “we have also tried to link up with the colleagues working in the DHIS2 platform. We want to get immunization data integrated into that platform”.

On vaccine stock out, he noted that the latest data on JRF indicate that countries still experience stock out. The good news, however, is that we are beginning to see improvements. He noted that efforts have been made to see if the stock out interrupt service and the results show positive association between stock out and interruption of services, thus this will be taken seriously.

One other area of focus is AEFI case monitoring. He reported that there are 25 countries with systems in place to monitor AEFI cases. Most of the cases seem to appear in a few countries. But the truth is that many countries are not reporting cases. It is thus important that we support countries to build strong AEFI systems

In terms of funding he lamented that very few countries fund adequately their immunization programmes. He noted that a huge proportion of the countries in the Region fund <50% of the vaccine or immunization costs. Many depend on Gavi funding. This is not sustainable as the Gavi funds will eventually come to an end someday.

Some of the challenges countries are facing include:

- Inadequate country ownership particularly the political commitment to fund and support their immunization.
- A number of countries have their GDP increasing and graduating out of Gavi support
- In terms of SDG, it is important to strengthen immunization system. Efforts have been made to engage colleagues in civil society organizations. To support countries to own their immunization programme.
- Integration is also a challenge particularly as the SDGs become key focus of programming.

Way forward

- Continued high level advocacy and communication to ensure sustained support for immunization:
 - Accelerate the implementation of the ADI roadmap
 - Develop an investment case for immunization in Africa (with a continental approach)
- Consider a systemic approach for strengthening immunization services:
 - Integration of immunization in the broader health system strengthening agenda
 - Revision of the RED approach to cater for the needs of disadvantaged/marginalized populations
- Forster Integration to enhance the delivery of immunization through the life course continuum.
- Promote immunization research: policies to be based on evidence and emerging local & global issues.
- Continue the implementation of the Regional data quality strategy

Figure 4: Way Forward for Addressing Challenges to Immunization Coverage and Equity in AFR

Improving Immunization Coverage through Equity Lens

Dr Rene Ekpini, Regional Adviser Health UNICEF WCARO

Dr Ekpini, the presenter, called on participants to forget numbers but think of men, women and children in villages that we work for. He asked how do we achieve coverage without involving them and argued that we need to reposition the communities. If RITAG will make recommendation to reposition communities as actors and not receivers then a lot would be achieved.



Figure 5: Community and its people served by immunization services

To achieve high coverage there is need to have a number of key factors in place. These include availability, accessibility, acceptability, contact and effectiveness. Every component has the dimension of equity meaning that everybody has access to services.

He noted that child and neonatal mortality have reduced considerably. All the same there are still the equity issues. Today we know deaths are more where mothers have low education etc. The gaps that exist between the poorest and the richest have implication for coverage and equity. In some cases the gap is widening. Again, he asked, how can we talk of global access without talking of equity?

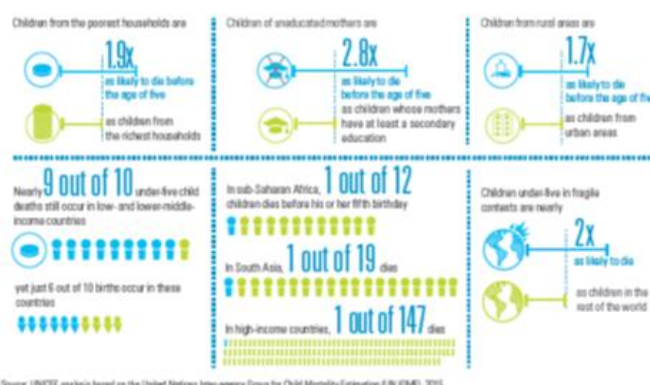


Figure 6: Disparity in child survival despite progress in service delivery

Out of the 8 countries with reduction in coverage, 6 are in West and Central Africa. Where there is stagnation, there is need to note that there is a considerable equity challenge to move from 80% to 90%. There is need to be vigilant when it comes to equity component of service delivery.

He further argued that the major bottle necks include some decisive elements of equity namely socio-cultural, economical, geographical, humanitarian and emergency all due to poor local governance and community accountability. He emphasized that we need to translate our recommendation to action. There is thus the need to strengthen communities to put governance

and community accountability in place to task the programmes to deliver. There is also poor organization of resources and services delivery to reach every child, the lack of integration leading to MOV; inadequate immunization cold chain and logistics management systems. We also have the problem of data management systems with inaccuracy

With regard to the Reaching Every District (RED) approach, the presenter mentioned that RED is not the problem. The problem is how we implement it and how the equity is taken into account. He asked, “How can we bring micro planning in a decentralized approach?” Activities like monitoring should be taken to those concerned. We should capitalize on the experiences of polio. The last point is resource mobilization. One of the reasons RED is not implemented is lack of resources and poor prioritization. He noted that in this region we have outbreaks but we also have opportunities. Take into account governance, reposition communities, Take RED to the communities; translate accountability to the community level etc. He concluded by raising some issues for RITAG.

Addis Declaration on Immunization – Roadmap Development

Helena O’Malley, WHO/AFRO

In February 2016, WHO/AFRO & WHO/EMRO – in conjunction with the African Union and the Government of Ethiopia – hosted the first-ever Ministerial Conference on Immunization in Africa at the AU Headquarters in Addis Ababa, Ethiopia. This conference convened African political leaders as well as African and global partner - around the goal of advancing universal access to immunization in Africa in line with the Global Vaccine Action Plan. Ultimately, the conference was a galvanizing moment for immunization in Africa, bringing together over 1,000 stakeholders which resulted in a first-ever Declaration on Immunization signed by Ministers of Health or Heads of Delegation which includes 10 commitments and 4 calls to action.

Thereafter, WHO/AFRO & WHO/EMRO began working with partners to develop a roadmap outline for Member States to accelerate progress toward improving immunization across the continent by supporting the effective implementation of the Addis Declaration on Immunization (ADI). In September 2016, immunization partners and a number of Member States met at WHO/EMRO (Cairo) to develop roadmap strategies and discuss monitoring and accountability systems. From September to December 2016, in consultation with technical experts and stakeholders, WHO and partners have developed a draft version of the roadmap which will be shared with Member States for their feedback in January 2017. The aim is to finalize the roadmap by early February 2017.

The ADI roadmap’s primary target audience is Member States who will lead the roadmap implementation. Universal health coverage will be the mainframe to work from to ensure universal access to immunization as a cornerstone for health and development in Africa. The roadmap will allow all stakeholders to harmonize and coordinate our efforts by supporting

Member States fully achieve the 10 commitments as outlined in the Addis Declaration on Immunization.

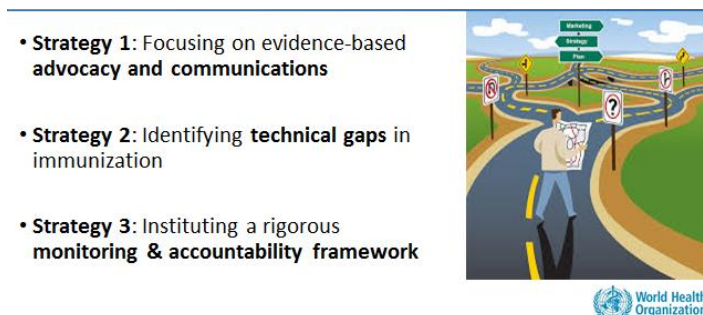


Figure 7: Road map to the ADI

In terms of structure, it focuses on evidence based advocacy and communication as well as identifying technical gap in immunization and instituting a rigorous monitoring and accountability framework. Each of these 3 strategies was developed into approached. For instance the advocacy and communications strategy has 4 approaches etc. She also highlighted the next steps.

Comments and observations

RITAG noted the challenge in repositioning immunization in HSS under the umbrella of service provision. This will need to be specified at the country level. There may be best practices too. They also noted that in the GAVI fund there are HSS funds and wondered if the funds can be integrated.

It was also noted that GVAP and the ADI declaration do not seem to be synchronized. The RITAG noted that there are three plans now, yet reference is not made to the original plan. How does the jigsaw of the different plans work together? The RITAG also raised concern on how the different framework of accountability work together

In terms of coverage, the question was raised on whether the reasons for the missed children are known. The RITAG called for a careful analysis of the profile of the missed children in terms of gender, education, birth order etc. it may be country specific. They also wondered on why there is the stagnation, called for case studies in countries declining or flat or stagnating

RITAG recognized that equity is key to the Sustainable Development Goals (SDG). They demanded that communication tools should look at. They also emphasized the importance of community health worker mobilization. This is linked to community engagement; demand; and hesitancy and refusal. The question that arose at this point is who does community engagement. The health workers are not trained to do this

Following the discussions, RITAG made some recommendation to guide the process of the

ongoing polio transition planning. The RITAG also made recommendation on way of addressing the challenges of achieving high immunization coverage and equity in access to vaccines and immunization services in the Region.

3.3 For Discussion and Decision

3.3.1 Measles/Rubella Elimination Strategies for the WHO African Region

Challenges in Attaining Measles/Rubella Elimination Targets

Dr Balcha Masresha, WHO/AFRO

The African Region adopted a measles elimination goal for 2020 with targets of at least 95% MCV1 coverage at national and district levels. The presentation thus opened with brief update on the performance of the Region on these targets. It showed that the total number of cases has significantly declined over the years. Routine immunization coverage has shown steady increase from 2000 to 2009. However the presenter noted that there has been stagnation between 2009 and 2015.

The criteria is that countries should have had sustained high coverage for two years before they can introduce MCV2. The Region has been conducting SIAs in countries with low coverage because of the small number of countries, which introduced MCV2 coverage has remained low. Twenty four of the 47 countries have MCV2 included in the routine immunization. Despite the fact that the MCV2 countries had high coverage of MCV1 the MCV2 has been generally low.

Some of the challenges faced by countries in increasing MCV2 coverage include:

- Informal rollout of the MCV2 introduction despite the fact that it is for different age group. No systematic sensitization or training of staff conducted to that effect.
- Recording and monitoring tool were not updates.
- Program has not fully implemented vaccination beyond 1st year of age.
- Different antigens used for MCV1 and MCV2 leading to wastage and confusion
- Missed opportunities for MCV because of minimum number of children required to open a vial

There are nine countries that introduced MR into their routine EPI. Eight countries did MR SIAs in 2016. With regards to campaigns and due to availability of fund through Gavi, more and more children are reached in catch up campaigns. There are however some issues with campaign quality and level of local resource mobilization. Only 3 countries that conducted SIAs have all their districts achieving the targeted coverage.

- 9 countries with MR in routine EPI
- MR SIAs in 8 countries in 2016

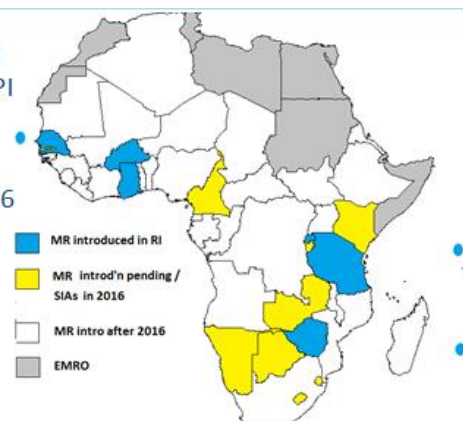


Figure 8: Status of Measles/Rubella Vaccine Introduction

With regards to surveillance, 44 out of the 47 countries have case based surveillance. Seventeen countries met both target while 16 countries meet 1 target while the other countries missed both. Measles surveillance has depended largely on polio resources and if the ramp down is not well managed it may impacted negatively on the achievements.

Table 1: Summary status of measles elimination against the milestones

Indicator : No. (%) of countries with...	RISP milestone for 2015	Regional Status
MCV1 $\geq 90\%$ nationally and $>80\%$ in all districts.	90% nationally in at least 20 countries	• 12 of 47 (26%) countries (WUENIC).
MCV2 in EPI	22 countries	• 24 of 47 (50%) countries
MCV2 $>90\%$ nationally		• 3 of 23 (13%) countries (WUENIC).
RCV in EPI	10 countries	• 9 of 47 (19%) countries
$>95\%$ SIAs coverage in every district		• 3 of 31 (9.7%) countries (which did SIAs in 2013 – 2015)
Measles incidence < 5 cases per million population.		• 22 of 44 (50%) in the last 52 weeks as of 30 Nov 2016
Measles incidence < 1 case per million population.		• 13 of 44 (30%) in the last 52 weeks as of 30 Nov 2016
Targets met for both principal surveillance performance indicators	100%	• 19 of 44 (43%) in the last 52 weeks as of 30 Nov 2016

Table 1 gives the summary achievement on the elimination targets. This revealed gaps and more work to be done. The presenter thus proceeded to enumerate the challenges. These included plateauing of MCV1 coverage, lack of funding, poor quality of SIAs among others. He also discussed opportunities that exist to ameliorate the situation.

Report of the External Evaluation of the Measles Elimination Strategy 2011-2020 in the African Region

Dr Ben Nkowane, Independent Consultant

The chair of the external evaluation team presented the TOR for the mid-term evaluation. He noted that the team came up with 25 recommendations that fall into five groups. He also highlighted the steps and processes that were involved in the exercise as well as the objectives of the measles elimination strategy in the African Region. He presented the guiding principle for the strategy implementation included and the milestones for elimination at the mid-term evaluation. In presenting the results, he noted the wide gaps between targets and the realities on the ground.

Table 2: Measles case based surveillance performance in AFR. 2012 - 2015

Category	2020 target	2013	2014	2015
Non-Measles Febrile Rash Illness rate	≥ 2 per 100,000 pop'n	2.9	3.0	2.5
% of districts reporting suspected measles cases with blood specimens	$\geq 1/100,000$ At least 80%	78%	77%	82%
% of suspected cases with adequate blood specimens	at least 80%	78%	85%	82%
Incidence (% countries per million population)	< 5 per 100%	53%	48%	77%
Incidence of confirmed measles per million population	< 1 per million	76.9	40	39.4

Table 3 also presented a summary of progress towards the African Regional targets for measles elimination.

Table 3: Summary of progress towards the African regional targets for measles elimination at mid-term 2015

Indicator	Regional Status in 2015	Comment
No. (%) of countries with MCV1 \geq90% nationally and >80% in all districts.	12 of 47 (26%) countries with MCV1 of 90% or more according to the WUENIC.	District level coverage data is available only in the country reported admin coverage data, and not all countries have submitted reports on proportion of district coverage.
2. No. (%) of countries with MCV2 >90% nationally	3 of 23 (13%) countries with MCV2 of 90% or more according to the WUENIC.	
3. No (%) of countries with RCV in their routine immunization programme	9 of 47 (19%) countries	
4. No. (%) of countries conducting SIAs with >95% in every district.	3 of 31 (9.7%) countries which did SIAs in 2013 – 2015, and which reported on detailed coverage data have achieved >95% admin. coverage in every district	
5. No. (proportion) of countries with measles incidence less than five cases per million population.	23 of 44 (52%) in 2013; 21 of 44 (48%) in 2014; 25 of 44 (57%) in 2015	Three countries (Seychelles, Sao tome & Principe and Mauritius) have not yet established case based surveillance for measles.
9. No. (%) of MCV SIAs that include additional child health interventions	26 of 35 (74%) SIAs between 2013 – 2015 have included at least one additional child survival intervention	

Comments and observations

RITAG acknowledged that the assessment is very helpful. It also suggested that there is work to be done in support of this review. What comes out very strongly is weak country ownership and governance. RITAG noted the need to reflect on those that are likely to achieve the target and those that are not. Several suggestions were made here, namely to document the cause of poor performance. RITAG also noted the issues with active surveillance.

The RITAG wondered if this is not right time to consider the establishment of a regional verification commission. Discussions were also held as to when the Region could decide to set a rubella elimination target? It was also resolved that there should be recommendation to the NITAGs

Concern for funding was also raised. Many countries depended on polio. What will happen after the polio funding is gone? To frame this as an argument, RITAG requested for a country analysis. The other thing is to frame the funding discussion as a health system issue as oppose to a single programme issue.

The RITAG also talked about countries planning a transition phase which will outline what is required in the next five years, arguing that donors may relate more with such an approach. It was suggested that such planning should highlight the inadequacies in the stock and also contain information human resources needs. The RITAG members also suggested an adoption of an approach that is integrative and not present SIA in conflict with routine immunization.

The RITAG made recommendations to address the observed uneven progress and challenges for measles elimination with the majority of countries in the region failing to reach 90% coverage for MCV1 and with much lower coverage for MCV2, among others.

3.3.2 Polio Eradication and Endgame Strategy

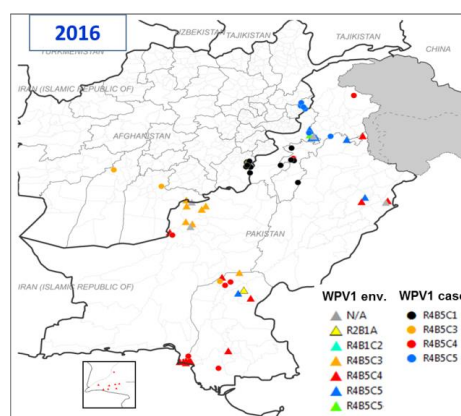
Global Polio Updates – Including IPV Vaccine Supply and Transition Overview

Dr Michel Zaffran, WHO/HQ

The presentation looked at the impact of GPEI on the progress of WPV eradication between 1988 and now. Dr Zaffran noted that this year recorded only 34 cases against 76 cases this time last year, the lowest number of reported cases ever globally.

Pakistan and Afghanistan recorded the lowest cases ever. Overall situation has improved in Pakistan and Afghanistan. However, some concerns were noted with cross border issues for instance.

With regards to the transmission in 2016 he noted that results from both environmental sampling and AFP in Pakistan still show active transmission. No positive environmental samples from Afghanistan were reported in 2016. Five separate VDPV type 2 events from Pakistan: Quetta (4, pending mOPV2 response), Hyderabad (fIPV response), Lahore (iVDPV).



Most recent cases - AFG: 12 Oct., PAK: 3 Nov.

Figure 9: AFG-PAK epidemiological block: WPV1 by genetic cluster, 2016

However, genetic sequencing of virus clusters in 2016 revealed diminishing number of chains of transmission, implying decreasing number of active virus clusters from 8 in 2015 to 7 in 2016. He concluded that the situation has improved as we now have decreased cases & positive environmental samples. He noted that strong Emergency Operation Centers (EOCs); strong coordination between the two national programs and National Emergency Action Plans (2016-2017) have been operationalized and kicked off. The outstanding concerns are deteriorating access in north-east Afghanistan (Kunduz); outbreak in south KP / FATA – southeast Afg. Block and weaknesses in surveillance at district level in Pakistan.

With respect to the Nigeria and Lake Chad region he noted the outbreak of viruses in Nigeria. These included four WPV1 cases reported in Borno in the last three months – all ‘orphan viruses’; 2 cVDPV2 isolated – also ‘orphan viruses’. These represent hundreds of infections, and years of missed transmission. All cases related to areas where the polio program stopped immunizing 2+ years ago because of inaccessibility due to Boko Haram threat. Regional public health emergency and Coordination centre was established in N’djamena, Chad with representatives of the 5 countries around the Lake Chad Basin. Five rounds of Multi-country outbreak response targeting over 40 million children were implemented.

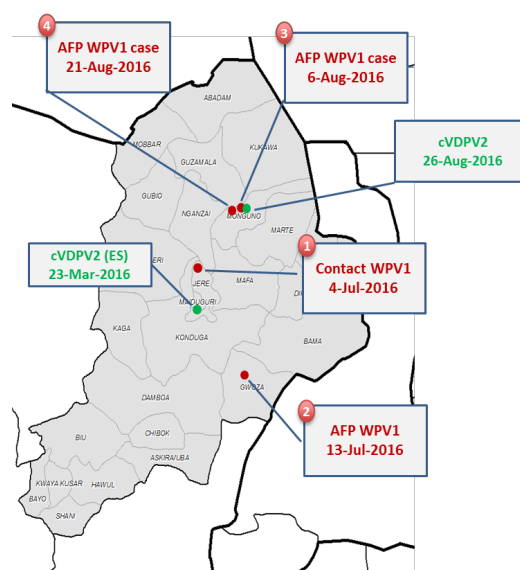


Figure 10: WPV outbreak in Borno State, Nigeria

The presentation also highlighted the important lessons learnt from Nigeria. Some of the lessons highlighted include need to look 'beyond indicators'; and look at cohort of susceptible children in specific groups (IDPs, Refugees, ‘locked in’ groups, etc...). Others include additional surveillance initiatives including mapping inaccessible settlements, expansion of environmental surveillance, geocoding of AFP cases and community involvement; and additional SIAs initiatives with hard to reach strategies and Permanent Transit Point Vaccinations.

The presentation also looked at implementation status of the other three objectives of the polio eradication and endgame strategic plan. In specific terms, he mentioned that the globally coordinated switch was a success and all 155 countries/territories using tOPV switched to bOPV in a synchronized manner. However, he flagged the need to stay vigilant for WPV2, having recorded 23 VDPV2 events since the switch. Unfortunately, IPV supply continues to decline due to production issues with both suppliers. This has impacted Tier 1 and 2 countries. He also noted the fact that SAGE is aware of this challenge and has made recommendations to guide operations.

With respect to containment, he noted that 24 countries have reported hosting 58 designated poliovirus essential facilities (PEFs). And with regards to polio transition, he enumerated the process of development of strategies for sustaining the polio free world. This strategic plan defines the future state (technical and programmatic) for a polio-free world. The TMG will coordinate the implementation of the Post-certification Strategy. He ended the presentation with a highlight of the current priorities for the GPEI.

Polio Update in Africa – focusing on the lake Chad Basin Region and other risks

Dr Pascal Mkanda, WHO/AFRO

Dr Pascal noted that the update is looked at in three ways. These include wild poliovirus type 1; circulating vaccine derived poliovirus and emerging VDPVs after the global switch. He then proceeded to present the emergency response to the poliovirus outbreak in Nigeria. He then enumerated the various steps taken in response to these outbreaks to include:

- Establishment of the Lake Chad Polio Task Team in August 2016 to coordinate outbreak response
- Ministerial Declaration of the wild polio outbreak in Nigeria as public health emergency in August 2016
- 5 synchronized polio outbreak rounds have been conducted
- Review of the outbreak responses in October - November 2016 to ensure interruption by end of Dec. 2016
- AFRO mechanism for monitoring recommendations implementation in place
- Reaching children for polio campaign and surveillance in inaccessible areas of \Lake Chad Basin

He also discussed other initiatives including strengthening surveillance in areas with gaps (inaccessible and accessible areas). He touched on AFP surveillance performance challenges in the Region in the last 12 months. According to him, some of the remaining surveillance challenges are in localized areas with insecurity hindering reach for surveillance activities; competing outbreaks and reliance on polio staff for response; weak health systems and logistic challenges for transportation of specimen; not prioritizing polio after being polio-free for many years; incorrect geographical location of AFP cases skewing actual performance. He then listed initiatives to strengthen surveillance in areas with gaps irrespective of their accessibility.

On objective 2 of the polio eradication and endgame strategic plan, he discussed issues relating to global IPV shortage; intradermal fractional IPV (fIPV) use in campaign and routine immunization settings. Other issues he touched on included responding to de-novo VDPV2 versus the risk of using a live vaccine (mOPV2) with a threat of new VDPVs emergence. He also noted the need for continues vigilance for Sabin type 2 isolation and response.

On Objective 3 he noted the challenges of Phase 1b laboratory containment in 2016. According to him, while phase 1a was completed in all 47 countries with South Africa as a poliovirus essential facility (PEF), the National Authority for Containment (NAC) has not yet been established and trained. He flagged the need for timely finalization of the inventory and survey of bio-medical labs for Phase Ib containment and also stressed the reluctance by bio-medical research institutes and surveillance networks (rotavirus, influenza) to destroy samples, he called for intensification of discussions and advocacy with research institutes

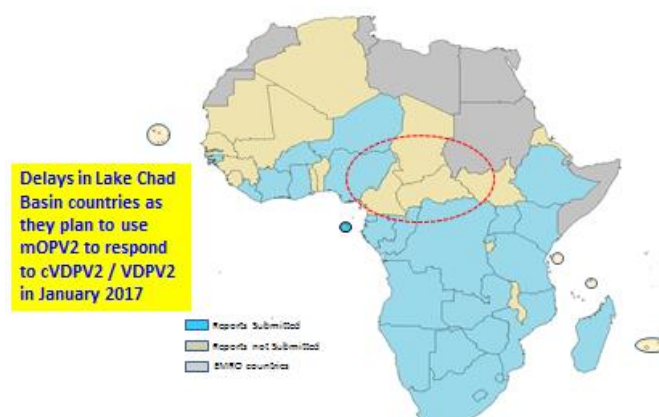


Figure 12: Status of Phase 1b Laboratory containment in African Region by 10 Dec 2016

GPEI Ramp-Down and Transition Planning in the African Region – UNICEF & WHO Perspective

Ms Helena O'Malley, WHO/AFRO

The presenter provided highlights of the progress to date. She enumerated the seven indicators of the transition planning process, and against these indicators she presented the performance levels of different countries. For instance communication to government leadership and appointment of governing management team are accomplished in all the countries. Similarly most countries have mapped the available polio assets. Few countries have mapped countries priorities while many others are still in the process. Majority of the countries are yet to start working on the last three indicators.

On polio ramp down, she made comparisons between the 2014/2015 funds distributed to WHO/AFRO including polio and Ebola activities, and 2014/2015 funds distributed to AFRO less polio and Ebola funds. It showed that 44% of the overall budget was for polio. On the average 22% of polio funds go to core staff while 13% and 65% are for surveillance and SIAs respectively. She also showed a graph of polio funded core staff and their locations.

Furthermore, she presented an analysis of the estimated time allocation of polio personnel by country. The countries included those with heavy GPEI investment, namely Afghanistan, Angola, Chad, DRC, Ethiopia and India. Others included Nigeria, Pakistan, Somalia and South Sudan. On the average therefore, she noted that staff spent 40% of their time on routine immunization related activities.

She gave the country ramp-down statistics in 4 waves. Wave 1 (2017): 117 “core staff” termination letters dispatched by end-2016 (Lake Chad Basin countries exempt); Wave 2 (2018): Termination letters dispatched by end-March 2017; Wave 3 (2019): Termination letters dispatched by end-March 2018; and Wave 4 (2020 & beyond): What are core polio functions that remain in post-eradication era? Elaborating on Wave 1, she noted that there will be 117 “core staff” termination letters dispatched by end-2016. Key brunt of terminations will include: Angola, DR CONGO & Ethiopia (80 staff functions).

Remainder 37 functions are in: B. Faso, Congo, Cote d’Ivoire, Eritrea, Kenya, Liberia, Madagascar, Mali, Mozambique, Rwanda, South Africa, South Sudan, Tanzania, Togo, Uganda, Zambia. It is important to note that the transition process is currently on hold in Nigeria and Cameroon due to the ongoing outbreak response in Nigeria & the Lake Chad region, and Nigeria’s reclassification as an endemic country

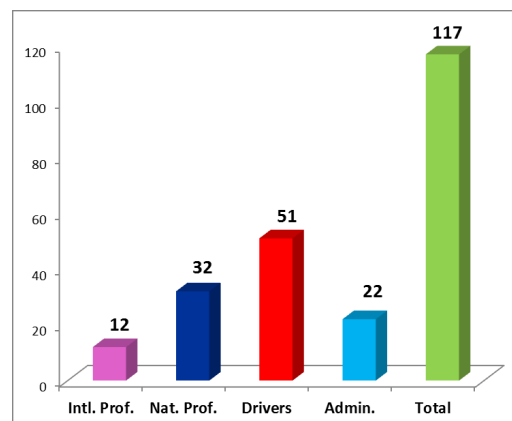


Figure 14: WHO/AFR Ramp-Down – Wave 1

Comments and Observations

The RITAG noted that the situation in the Lake CHAD region is very dangerous and stressed that all the people working there deserve support, good will and prayers from immunization partnership including the RITAG members. The health worker operating in those locations should be recognized as heroes without doubt. It was stressed that inside Lake Chad there are over 1000 islands with many children and only accessible from Chad. From the Nigeria side, there are hundreds of such inaccessible islands. The populations are very mobile and scattered all over Nigeria. Activities are not synchronized with the Nigeria government. There is a need to have a policy to get the countries synchronized. RITAG also noted the lack of synchronization in community engagement and management of the refugee situation across countries in the Lake Chad Region. The RITAG called for caution about other areas like the CAR, South Sudan and concluded that the job is not yet done. The RITAG also discussed the threat of other outbreaks in places like Nigeria and transmission to Ethiopia and Somalia. They equally discussed the outbreak in Madagascar and noted that the response was precipitous

With regards to polio transition planning, it was noted that the risk of more outbreak should be carefully assessed to guide the transition planning and ramp down. They wondered if the transition plans considered new risks with inaccessible and migrating population as well as nomads. It was noted that whereas countries have been informed of the transition, the messages do not seem to be going across. They wondered if the transition is premature given the risks and the existence of IDP, inaccessibility of the population without detailed country planning. They called for rationales for longer period. It was noted that 50% of the staff time is spent on other

activities. It was then suggested that new donors should be engaged. To sustain more support it was argued that the problem should be broadened. Partners present at the meeting agreed that there is a disconnection in the planning and budgeting. They expressed appreciation for the transition in IMB but were worried with the quality of outbreak response. They called for independent assessment of outbreak response verification of the children access to the vaccines in line with the guidelines. Members also noted the importance of security and security compromised areas, mentioning Nigeria as a typical example. They called for more emphasis on cross border and transit teams.

Finally, the RITAG called for independent review of the impact of transition on immunization programmes. In addition to an independent evaluation of WHO, there should be an evaluation of what is required for lagging countries.

On IPV fractional dosing and off label use, the RITAG noted serious constraints on supply. It also noted SAGE recommendation. They also noted the challenge to dosing twice but may have to use fractional dosing if supply worsens. They noted the need to sensitize the NRA.

Finally, RITAG made recommendations addressing issues affecting inaccessible areas as well as importation of polioviruses from countries with continued transmission. The recommendations also touched on support for countries to increase vaccination.

3.3.3 Eliminating Yellow Fever Epidemics in Africa

Global Strategy for Eliminating Yellow Fever Epidemics

Dr Richard Luce, WHO/HQ

The presenter noted that the new global strategy for eliminating YF epidemics builds on lessons learned from previous control efforts in an integrated manner. This is a 10 year global strategy 2017-26 for 34 and 13 countries at risk in Africa and the Americas respectively. The new strategy, which is ready for adoption by the WHA in 2017, is comprehensive and comprising of both risk evaluation and preventive vaccination strategies.

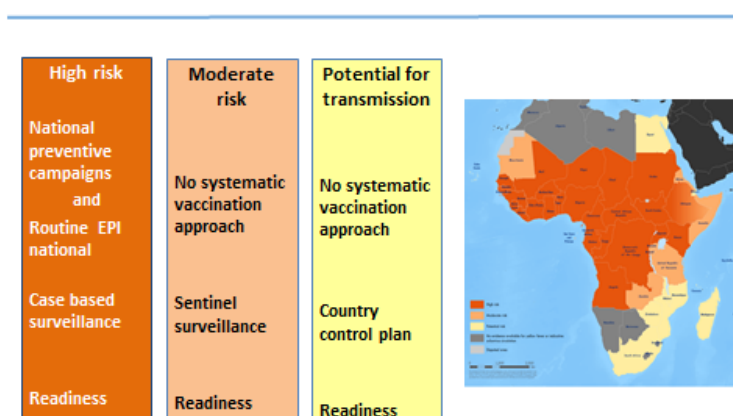


Figure 15: Three categories of risk

He stressed that strategic objective 2, which focuses on preventing international spread seems to be a straight forward mechanism but the international checking of vaccination status is proving a challenge. On the third strategic objective to contain outbreaks rapidly, he presented the situation

with surveillance and lab capacity. The strategies include building capacity for surveillance and laboratory; increase diagnostics capacity and improve on regional database management. In summary, it is clear that early YF control efforts were effective and EYE is updated for long term and comprehensive strategy. It has been largely risk based rather than endemic zone approach. Vaccination has been through a combination of routine and campaign. YF stockpile is maintained for response and vaccine manufacturers

He presented the next steps for the African Region. These include to:

- Adapt the global YF strategy to regional level
 - Validate and disseminated to countries
- Develop a regional implementation framework for the global strategy
- Present the framework to the next RC meeting for adoption and endorsement

Challenges in Eliminating Yellow Fever Epidemics in Africa

Dr Mamoudou Djingarey, WHO/AFRO

The yellow fever vaccine is efficacious and one shot protects for life. Ironically it is not used in all at-risk countries. Dr Djingarey, the presenter, noted that the suppliers are already able to supply more than they had in the past and have potential for reaching future requirements. This year 2016 supply to UNICEF exceeded 50 million doses. If suppliers are able to utilize their new installed capacity, then there is hope to reach the forecasted target doses.

Unfortunately there is inadequate funding for operational activities. He gave detail of other challenges that exist. These include increasing urbanization in endemic areas, low population immunity and high densities of the *Aedes aegypti* mosquito vector (increased likelihood of large urban outbreaks, resurgence of vectors); inadequate funds for field operational activities; risk assessment pending in countries considered as high risk; and limited stocks of the YF vaccines globally. Others include achieving the YF vaccine coverage target (90%) per the AFR regional strategic plan for immunization (2014-2020); organizing preventive mass campaigns; introducing YF vaccination in remaining EPI programs that do not provide it; delay in lab confirmation and surveillance gaps; and how to decrease the delays of 3-4 months between onset/detection and conducting response campaigns.

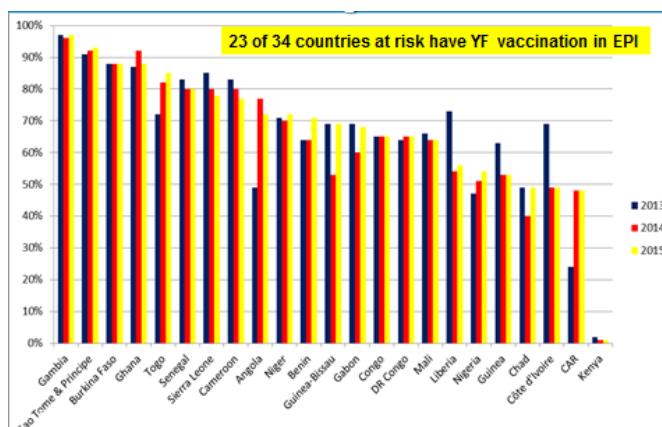


Figure 16: YF-WHO/UNICEF estimated national immunization coverage in AFR 2013-2015

Comments and observations

The availability of the vaccine was discussed exhaustively. Members wanted to know the basis for the estimation. Responding to this concern it was mentioned that it was based on risk assessment. However, it did not take into consideration what is happening in China. All the same, this is a disease that can be easily managed. In summary, this is the need based on the current production.

The RITAG noted the EYE strategy as presented as well as the SAGE recommendation on fractional dose. The RITAG also reviewed the availability of the vaccine and took note that the EYE strategy has taken into account that dimension. The RITAG recognized the dearth of suppliers and encouraged dialogue with the manufacturers. As the Regional office move from the EYE strategy to developing regional framework for implementation of the EYE strategy, RITAG requested that the document be shared with the RITAG members for comment before completion

The RITAG recognizes that while it is not possible to eradicate yellow fever, elimination of epidemics is feasible and is essential against the backdrop of global warming, the changing distribution of *Aedes aegypti*, migration and urbanization. It thus made recommendations to address the challenges and facilitate the realization of the programme goals.

3.3.4 Maternal and Neonatal Tetanus Elimination in Africa

Progress towards MNT Elimination in Africa

Dr Balcha Masresha, WHO/AFRO

Presenter started by flagging the point that the MNT elimination targets have been missed many times since 1995, 2005, 2010 and 2015. He presented the key strategies to MNT elimination as highlighted in the GVAP (all countries to eliminate MNT by 2015) as well as in the Regional Immunization Strategic Plan (RISP) 2014-2020. He also reviewed the various elimination strategies and proceeded to elaborate on objective 4 of RISP which holds that “all countries to attain and validate elimination of maternal and neonatal tetanus by 2020” with clear milestones.

There is another recommendation that called on countries to shift from TT to TD. As of today only 14 of the countries have done this. Even among the 14 most of the countries are using both TT and TD simultaneously.

He listed some of the principal challenges to include low visibility of MNT, more visible

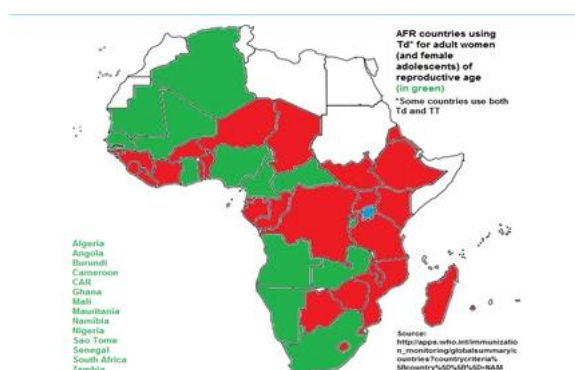


Figure 17: AFR countries using Td for WCBA, 2015

competing priorities; disease burden information not widely available, weak surveillance; lack of leadership/ champions; inadequate and unpredictable partner funding; rumours and cultural sensitivities, traditional harmful practices around delivery. Others were gaps in ANC, safe delivery services; and civil unrest/ conflict limiting access.

Comments and observations

RITAG members called for a careful review of the investment case to assess provision for the MNT elimination. There was concern with the reason for going back to the old schedule and the RITAG noted that this needs to be made clear to the countries. This issue of MNT programme being an orphan of the EPI but not well rooted in the Family Reproductive Health (FRH) programme is also a challenge. It was stressed that looking at countries that have attained elimination status and looking at long term sustainable approach we have to incorporate school based programming. This gives opportunity to reach the target population for the booster doses. This can be integrated with other school age interventions like deworming.

The group wondered if there is an algorithm to help the Traditional Birth Attendants (TBAs) to guide mothers on what services they should receive and whether it is possible to come up with some strategies that combine essential strategies for pregnant women.

Surveillance issues were also considered important. It was noted that disease and case based surveillance have been done, but the threat to surveillance with polio transition is very palpable. The other very strong message here is the integration with other child health services. RITAG noted the need to strengthen the recommendation for integrated services. Vertical donor funded programmes will weaken integration.

In terms of framing this, the other thing that came out is the MNT risk assessment and equity assessment. This will bring it in the context of the SDG. RITAG noted the serious challenge in this region including Nigeria. Uniject TT might be a useful technology for the hard to reach area else the emphasis should be on TD.

Finally the RITAG made recommendations to fast-track the development of the MNTE investment case as well as address other issues confronting the Region on its progress to attaining the MNTE goals.

DECLARATION ON UNIVERSAL ACCESS TO IMMUNIZATION AS A CORNERSTONE
FOR HEALTH AND DEVELOPMENT IN AFRICA

Doc. Assembly/AU/xx(XXVII)

The Assembly

1. **TAKES NOTE** of the proposal by the Federal Democratic Republic of Ethiopia on “UNIVERSAL ACCESS TO IMMUNIZATION AS A CORNERSTONE FOR HEALTH AND DEVELOPMENT IN AFRICA”,

RECOGNIZES that as the continent that has the youngest population of any region globally, developing the right policies and investments in health for youth, including investments in immunization, will position Africa to move into new opportunities that emerge from a demographic dividend,

2. **RECALLS** that Article 14 the African Charter on the Rights and Welfare of the Child stipulates that every child shall have the right to enjoy the best attainable state of physical, mental and spiritual health,

3. **ACKNOWLEDGES** that harnessing the demographic dividend through broad-based inclusive economic growth in Africa is also dependent on a healthy population; and that strong immunization programmes are a cornerstone of robust health systems that help to achieve universal health coverage which is critical for Africa to achieve the economic and development goals set by Agenda 2063,

4. **RECOGNIZES** that the economic imperative and benefits of reducing vaccine-preventable diseases and consequential deaths will improve overall health, empower our future generations and allow every person to achieve his or her full potential,

5. **REAFFIRMS** commitment to implement the Pharmaceutical Manufacturing Plan in Africa (PMPA) that will promote and invest in regional capacity for the development and production of vaccines,

6. **ENDORSES** the Ministerial Declaration on Universal Access to Immunization as a Cornerstone for Health and Development in Africa,

7. **CALLS UPON** Member States to support the implementation of the Declaration to ensure and facilitate universal access to immunization by allocating adequate domestic resources and securing new investments to strengthen national immunization programmes as well as mount strong advocacy campaigns to achieve the Global Vaccine Action Plan goals and overall health care delivery systems,

8. **FURTHER CALLS UPON** Member States in partnership with all relevant stakeholders, to negotiate with vaccine manufacturers to ensure and facilitate access to vaccines at affordable prices while increasing price transparency,

9. **FURTHER REQUESTS** the Commission, Member States, WHO and partners to facilitate the implementation of the Declaration and put in place a mechanism for follow up and regular reporting to the Summit to include a corresponding accountability framework.

Immunization Demand team
Division of Health Emergencies and Communicable Diseases (DEC)
Vaccine-preventable Diseases programme (VPI)
WHO Regional Office for Europe

2016 progress report

Contents

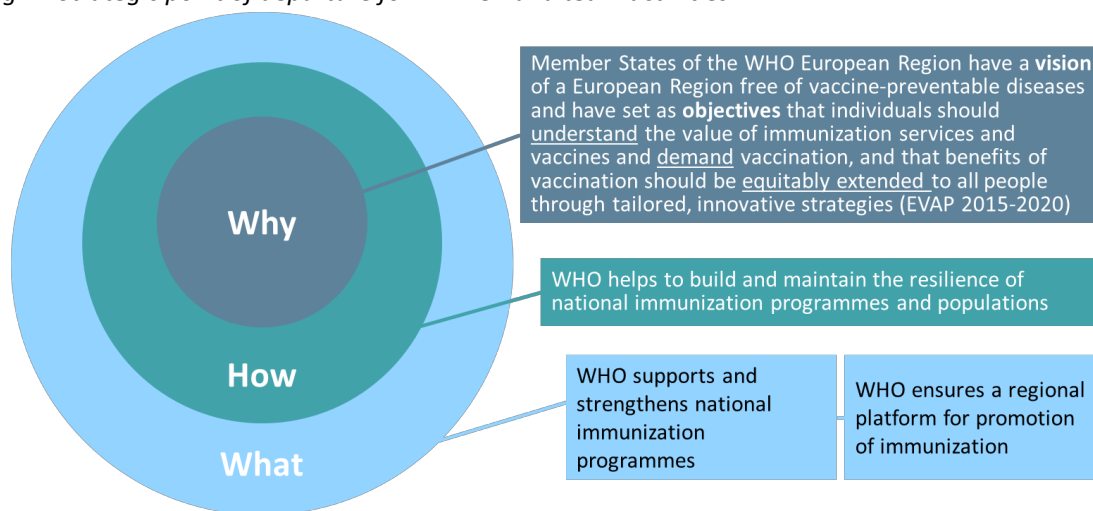
Contents	2
Background.....	3
Focus on resilience	3
Continuous development processes	4
Supporting national immunization programmes	5
<i>Tailoring Immunization Programmes (TIP)</i> behavioural insights approach	5
Vaccine confidence-building and crisis response.....	6
Support in response to disease outbreak and safety events	7
Intersectoral health education project.....	8
Responding to vaccine deniers in public	8
Country immunization communication reviews	9
HPV introduction communication	9
Polio Outbreak Simulation Exercise (POSE) training programme	10
Advocacy for sustainable funding of immunization programmes	10
“Wiser immunisers”: Online vaccination course.....	11
European Immunization Week (EIW)	11
Support for online communication about immunization.....	12
Networking in the immunization community	12
Public seminar on measles and rubella elimination.....	13
Ensuring a regional platform for promotion of immunization.....	14
Measles and rubella elimination target advocacy.....	14
European Vaccine Action Plan (EVAP) promotion.....	14
Publications and reports.....	14
Website.....	15
Social media.....	15
Further outreach	16
Continued work in 2017	17
Promoting EURO tools and approaches in other regions.....	17

Background

Responding to requests from Member States for technical support and guidance, and supporting the implementation of the European Vaccine Action Plan (EVAP), VPI’s Demand team in recent years has scaled up activities that aim to promote demand for vaccination and tailored strategies to ensure equitable extension of vaccination services.

In this area, technical support to national immunization programmes, development of guidance documents and tools and capacity building through training activities are supported by a regional platform for promotion of immunization which aims to increase public awareness, support work in Member States and among partners and increase WHO/VPI visibility.

Fig. 1: Strategic point of departure for VPI Demand team activities



Focus on resilience

The overall focus for these activities is to help build resilient national immunization programmes with adequate capacity, structures and mechanisms to ensure resilient populations that are fully and timely vaccinated and trust vaccination and health authorities.

Fig. 2: Resilient programmes and resilient populations

Resilient programmes

- have high coverage
- work long-term to ensure public trust in and knowledge of immunization
- know which population groups are sub-optimally vaccinated, understand the reasons behind, and are able to minimize barriers and maximize enablers to vaccination
- respond to denialism and crises and mitigate their negative impact
- protect and build immunization budgets through advocacy efforts



Resilient populations

- are fully and timely vaccinated
- have high levels of trust in vaccines and health authorities
- are less affected by and do not spread misperceptions
- are guided by evidence, not fear

Continuous development processes

Supporting materials and new projects are developed in consultation with Member States and leading experts. Some areas of work are still new – to WHO, global partners and Member States – and activities and materials are under continuous development and refinement, based on feedback from Member States and lessons learnt in the process.

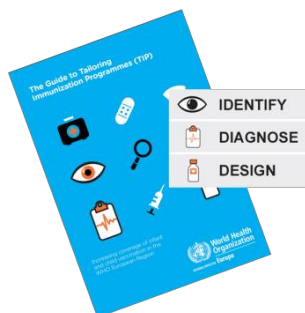
The Demand team is breaking ground in developing guidance and tools in areas where materials and activities have been weak or non-existent, or have had a broader focus. As a result, we are receiving considerable global attention and requests for collaboration from global partners and WHO headquarters and regions.

VPI's Demand team consists of two staff plus WHO consultants.

This report summarizes the work undertaken in 2016, structured in two sections reflecting the strategic foundation for our work: supporting national immunization programmes and ensuring a regional platform for promotion of immunization.

Supporting national immunization programmes

Tailoring Immunization Programmes (TIP) behavioural insights approach



With continued sub-optimal vaccination coverage and large-scale measles and rubella outbreaks in the Region, the need for tailored activities to reach susceptible population groups is evident. To support Member States in closing immunity gaps, TIP was piloted and rolled out during 2013-2016. To take stock of progress and lessons learnt and explore potential for new developments, a regional-level evaluation was conducted in 2016 with an external team of six leading global behavioural science experts, including two US CDC representatives. The evaluation, which will set the course for immunization behavioural work in the years to come, was informed by country missions, review of national and regional documents and an online regional survey.

The evaluation committee concluded that there is strong demand for the type of research addressed by TIP and that national TIP projects had added considerable value in a number of ways, including through community engagement and qualitative research, enhancing the ability of national immunization programmes to listen and gain an understanding of community and individual perspectives and allowing them to identify interventions responsive to the insights gained. Key strengths of the TIP approach were identified as the interdisciplinary stakeholder engagement; questioning of assumptions and collectively agreeing on who the susceptible groups are; considering changes to service delivery rather than focusing solely on communication; and WHO engagement and support.

The evaluation committee recommended that WHO help countries translate diagnostics into interventions, e.g. through enhanced local ownership, integrated diagnostic and intervention design, follow-up advocacy and incentives like seed-funding for intervention and evaluation activities. It was recommended to address the aspects of time requirements and investment of human and financial resources, e.g. through a needs assessment tool for countries and a shorter diagnostic exercise. The committee also made recommendations for new TIP materials and training activities. Along with the final evaluation report, a peer-reviewed publication is planned for Q1 2017. (The report is available at: <http://www.euro.who.int/en/health-topics/disease-prevention/vaccines-and-immunization/publications/2017/tip-evaluation-report-2017>)

As prompted by the Scientific Advisory Group of Experts on Immunization (SAGE) and the SAGE Vaccine Hesitancy Working Group, a TIP **Field Guide for global use** was finalized in 2016 by a team of researchers at the Wits University, South Africa, with the active engagement of the VPI Demand team. The Field Guide is an adaptation of the original European TIP guide and intended for use at field, district and community health levels in lower income settings. The Field Guide will be piloted in the Philippines in 2017 with engagement from WHO headquarters and the Demand team.

United Kingdom finalized its TIP project to improve vaccination coverage among the Charedi Jewish population (the ultra-orthodox) of North London (report launched in November 2016: <https://www.gov.uk/government/publications/tailoring-immunisation-programmes-charedi-community-north-london>). As part of the project, a range of sub-studies were carried out, including evidence of coverage in the community; evidence of disease prevalence in the community; evaluation of services provided at the community clinic; in-depth parent interviews; and segmentation of the population according to immunization uptake. The Demand team facilitated a stakeholder and community meeting in **London, United Kingdom**, in April 2016 to share and discuss the findings with community representatives and community service providers. Based on this, recommendations were made on ways to tailor local immunization services.

Germany continued its TIP project, finalizing three questionnaire-based sub-studies: identifying determinants related to parental intention to immunize preschool children against measles, mumps and rubella; exploring parental barriers to vaccination, as assessed by social medical assistants and paediatricians; and exploring determinants related to vaccine hesitancy among general practitioners. Next steps include a planned stakeholder meeting in Baden-Wurttemberg in 2017 to discuss and identify tailored service delivery solutions and explore potential additional research needs, at state as well as federal levels.

A partnership with **Finland** was initiated to conduct a number of TIP projects targeting susceptible population groups. An initial meeting was held in November 2016, and a stakeholder workshop is planned for early 2017.

There is considerable interest in the TIP tool and approach in Member States, and countries planning or considering TIP projects to start up in 2017 with support from the Demand team include **Armenia, France, Georgia and the Republic of Moldova**. Regional plans for TIP in 2017 include a summer school on behavioural insights at Erfurt University, the development of a new short- and long-term strategy and the establishment of a technical advisory and support function in the form of a technical advisory board or a centre of excellence.

The dedicated TIP webpage provides more information: <http://www.euro.who.int/TIP>

Vaccine confidence-building and crisis response



Following continuous requests from Member States for technical support in this area, the Demand team developed new guidance tools to support countries in building and maintaining confidence in vaccines and health authorities and responding to vaccine safety-related events or crises. The new comprehensive support package is a further development of a 2013 publication (Vaccine safety events: managing the communications response) and was developed in collaboration with the Network on Health Communication at Erfurt University, **Germany**. The package contains the following elements, to be launched in Q1

2017:

- “Vaccination and trust” background document: Defines and describes the key concepts and theoretical elements pertaining to communication and building confidence in vaccines and vaccination, both in ongoing work and during a crisis. It provides a foundation and knowledge

base to prepare communication strategies and crisis plans, or to plan and conduct training workshops.

- Online library of supporting documents: Contains documents with tangible guidance for specific situations, such as templates for communication strategies, press releases and messages; tips for spokespersons and guidance on preparing for interviews and journalistic tactics; guidance on stakeholder management and setting the media agenda; checklist for planning new vaccine introduction communication and much more.
- Training programme: Includes a planner and facilitator guide, training modules, case examples for group work and a one-day simulation exercise.

During the process, 6 subregional or in-country training workshops have been conducted in this area, including 2 in 2016: 30 May 2016 in Belgrade, **Serbia**, and 21–25 November 2016 in Budva, **Montenegro**, with participants from **Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Republic of Moldova, Montenegro, Romania, Serbia, Tajikistan, Ukraine and Uzbekistan**.

National immunization programme managers, national regulatory authority decision-makers and ministry of health communications staff attended these workshops, which were based on comprehensive training exercises, case-based scenarios and a one-day simulation exercise. They aimed to provide practical, informative strategies and tools to help plan and manage a communications response following a safety event. Workshops also provided opportunities to share vaccine safety and crisis communications experience from across the Region and have informed the development of the new support package. A video from the **Montenegro** training, which included training on vaccine safety in general, can be found here: <https://youtu.be/OrOTOb4dWck>.

Support in response to disease outbreak and safety events

Supplementing VPI support in other technical areas of work, the Demand team provided technical communication support to a number of Member States in 2016 in response to disease outbreaks and vaccine safety events. Communication support packages and messages were developed for **Belarus** in June 2016 following the death of a 6-year-old girl shortly after receiving an MMR booster, and for **Serbia** in March 2016 in response to negative media coverage and public debate in relation to a new vaccination law. Comprehensive communications support was provided to **Romania** during November–December 2016 in response to a major measles outbreak with 9 deaths coinciding with the passing of a new vaccination law. This support included a consultant mission on 20–27 November 2016 and support for the development of a communications strategy and action plan and several communication materials for public target groups.

Following ongoing negative debate on the HPV vaccine in a range of countries in the Region, vaccination rates have dropped in several countries. Responding to this challenge, the Demand team is providing direct technical support for a strategic response from national health authorities. Supplementing the direct support provided to individual countries, the Demand team organized an informal consultation on 10 October 2016 for **Denmark, Ireland and the United Kingdom** in Copenhagen, **Denmark**, bringing together regional and global experts and peers with technical knowledge and experience within vaccination and confidence-building. Subsequently, a *HPV group of peers* was established, including also the **Netherlands**, with bimonthly telephone conferences

organized by the Demand team. **Austria** has expressed interest in joining the group and will be included in the next teleconference on 10 February 2017.

The Demand team has also initiated the development of a communication support package on HPV, including two animated information videos, originally developed by the Danish Medicines Agency and adapted for use in English and Russian (links pending). The videos and other products include key messages on HPV, the HPV vaccine and HPV vaccine safety for adaptation in Member States, segmented per target group. Work on this package was initiated particularly because existing support opportunities in this area for parents and adolescent girls in local languages were deemed inadequate. A global expert has been engaged, and messages are expected to be finalized early 2017. All products will be posted on a new HPV section of the WHO/Europe website.

Intersectoral health education project

On the recommendation of the European Technical Advisory Group of Experts on Immunization (ETAGE), the Demand team is in the process of developing a school immunization module. The school setting offers unique opportunities to reach key target groups, and the approach strengthens intersectoral work within the Region at a time when healthcare reforms increasingly focus on interdisciplinary approaches to service delivery. Using digital and innovative learning methods, the module is intended to reach not only school children but their parents as well, as the learning mostly takes place at home, with reinforcement of learning in the classroom.

As the Demand team is breaking new ground in this intersectoral approach and in applying proven approaches to a new context, extensive desk and exploratory research and consultation with technical experts in various fields was a critical first step during 2016. Based on this process, which was aimed at learning from similar projects in other fields, obtaining insights into the educational systems of various Member States and gauging the potential interest and possibilities to apply an intersectoral health module in the national school setting, a concept paper was finalized in 2016. It was decided to pilot the school module in one country and subsequently adapt and roll-out regionally and globally based on an evaluation of the pilot.

Denmark was selected as a pilot country as its school system is in the forefront of using innovative learning methods, its vaccination coverage is below targets and it has experienced considerable negative public debate on vaccination in recent years. A partnership with the Danish Chief Medical Officer and the Danish Health Authority was therefore initiated.

A call for proposals was developed and six potential subcontractors were invited to develop a concept. It is expected that the pilot module will be developed and tested before the end of 2017.

Responding to vaccine deniers in public

To support national immunization spokespersons, the Demand team with support from vaccination, communication and science denialism experts developed a guide on facing vocal vaccine deniers in the public (<http://www.euro.who.int/en/health->



[topics/disease-prevention/vaccines-and-immunization/publications/2016/best-practice-guidance-how-to-respond-to-vocal-vaccine-deniers-in-public-2016](https://www.who.int/topics/disease-prevention/vaccines-and-immunization/publications/2016/best-practice-guidance-how-to-respond-to-vocal-vaccine-deniers-in-public-2016)).

The guide was developed based on a review of peer-reviewed journal articles in the relevant fields, which revealed the five key topics (such as questioning the necessity of immunization or promoting “healthier” alternatives to immunization) and the five key techniques (such as referring to fake experts or the application of false logic) that are most commonly used by vaccine deniers.

Reducing what might otherwise be seen as an overwhelming communication challenge to a manageable collection of topics and techniques, the guide presents a set of appropriate responses that can be used to debunk the misperceptions of the denier and win over the attention and trust of the audience.

The first edition of the guide was launched in May 2016 and tested in a pilot training during a sub-regional technical consultation on 31 May-1 June 2016 in Belgrade, **Serbia** with participants from **Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Montenegro, Serbia, Slovenia and the former Yugoslav Republic of Macedonia**. A second edition of the guide was developed based on lessons learnt from this workshop and used during a training workshop on 20-22 December 2016 in Copenhagen, Denmark with participants from **Bulgaria, Denmark, Ireland, Romania and the United Kingdom**.

Participant feedback to the training workshop and document was very encouraging, and indicative of a great need for support and guidance in this area. Further development of the guidance document and pilot trainings are planned for 2017. This will include a workshop in German for stakeholders from German-speaking regions and countries in Q2.

Country immunization communication reviews



Responding to requests from Member States, the Demand team offers direct technical support in the form of national immunization communication review missions.

A structured tool has been developed for these reviews which are conducted to assess all communication-related efforts in a national immunization programme, including capacity, tools, processes and management and vaccine safety and crisis preparedness. Review conclusions are summarized in a short and action-focused report with clear recommendations and proposed next steps towards the establishment of appropriate communications structures and collaboration, capacity building and improved and impactful communication efforts.

Communication review missions were conducted in **Slovenia** in January 2016 and in **Romania** in April 2016. The outcome of reviews conducted in 2014-2015 was monitored and follow-up consultant support was provided to support the implementation of recommended activities.

HPV introduction communication



Building on the lessons learned from the introduction of HPV vaccination in a range of countries worldwide, where negative media and public debate and alleged adverse events have caused decreases in coverage or caused the HPV introduction programme to fail altogether, VPI is providing comprehensive support to Member

States that are planning to introduce HPV vaccination in 2017: **Armenia, Georgia and the Republic of Moldova**. This support from VPI includes the above-mentioned HPV communications package (with various communication products on HPV vaccine, including Q&As, animated information videos, HPV statements and key message, fact sheets and dedicated HPV pages on the WHO/Europe website including references to global supporting materials).

To support preparations and help develop strong introduction communication strategies, the Demand team has developed a field guide on rapid qualitative research and communication strategy development for use in Member States. The guide was pilot tested in Armenia in November 2016, and the final version is expected to be launched in Q1 2017 along with training workshop activities for immunization managers and teams. The relevance of the guide goes beyond HPV and upon further testing and implementation will be promoted as a tool for new vaccine introduction in general.

Polio Outbreak Simulation Exercise (POSE) training programme



A comprehensive simulation-based training programme aimed at building national capacity to respond to polio outbreaks has been offered to Member States by VPI. A communications element offers technical guidance and advice on strategic communications planning, social and traditional media management and spokesperson skills, as well as a range of simulated situation exercises, including a media interview and even use of the telephone conference as a critical coordination mechanism

(http://www.euro.who.int/data/assets/pdf_file/0004/290407/Polio-Outbreak-Simulation-Exercise.pdf).

Following two sub-regional POSE training workshops in 2015, one training workshop was held on 27-29 August 2016 in Almaty, **Kazakhstan** with participants from **Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan**.

Advocacy for sustainable funding of immunization programmes



Aiming to strengthen financial sustainability of national immunization programmes through greater political and decision-maker prioritization and insight, WHO-IDEA together with the Immunization System Strengthening (ISS) Group completed and launched a support package on advocacy for sustainable funding of immunization programmes. The package offers guidance materials, capacity-building resources and tools for application in advocacy activities in Member States and is available in English and Russian in a web-based advocacy library:

<http://www.euro.who.int/en/health-topics/disease-prevention/vaccines-and-immunization/publications/immunization-advocacy-library>.

Following two subregional training workshops in 2015 to introduce basic concepts and sensitize national stakeholders to the importance of working strategically to ensure political and decision-maker support to immunization, next steps include in-country missions and technical assistance for the development of national advocacy and resource mobilization action plans. To support this process, WHO-IDEA in 2016 developed a template for a national action plan in this area, along with templates for national workshops and in-country presentations. On 30-31 March 2016 a consultant training workshop was organized in Copenhagen, **Denmark**. Consultants will be engaged to help

planning processes and stakeholder engagement in **Armenia, Azerbaijan, Georgia, Republic of Moldova and Uzbekistan** towards action plan development during 2017.

“Wiser immunisers”: Online vaccination course



As recommended by the European Technical Advisory Group of Experts (ETAGE), VPI in 2015 developed an online training course on immunization for health professionals together with the European Society for Paediatric Infectious Diseases (ESPID) and University of Oxford, Technology-Assisted Lifelong Learning (TALL). The online course is intended for any health professional involved in immunization and aims to enhance health professionals’ knowledge, commitment to immunization and confidence in communicating with caregivers. Students who complete the course earn continuing education credits applicable in all European Union countries.

Following a pilot for 40 participants in September-December 2015, the module was officially launched in Q1 2016 and ran for a third time in Q3-4. Student feedback has been overwhelmingly positive, with suggestions for change focusing particularly on increasing the engagement of tutors. The next steps for WHO will be to investigate options for translation and hosting of the course content in Russian and other regional languages, building of and provision of free-of-charge access to non-English versions, accreditation outside the EU, and securing ongoing financial and human resources support to administer the non-English versions of the course.

European Immunization Week (EIW)

EIW 2016 focused on highlighting progress towards regional elimination of measles and rubella and the need to maintain this momentum. As in previous years, the WHO Regional Director and HRH Princess Mary of Denmark lent their support to the initiative, this year in the form of a joint photograph and statement.

Support for national activities was provided in the form of a communications and social media packages, merchandising templates, fact sheets and infographics, and financial contributions for translation and special projects. Messages were broadcast by traditional and social media (see also below) and distributed through many settings, from ministerial conferences to patient waiting rooms. VPI staff participates each year in several national events, including technical and press conferences.



Over 100 national activities took place and materials were produced in over 10 languages. National initiatives were more visible in 2016 than ever before, thanks to launch of the new Immunize Europe Forum (see also below). In general, online interest in EIW materials and information increased substantially, with the number of visitors to the dedicated EIW subsite on the EURO website (www.euro.who.int) doubling from 13,000 in 2015 to 26,000 in 2016. Increased visits to all the vaccine-related pages, EIW press release, etc., ensure that the EURO website as a whole experiences a peak in usage during April each year.

A narrative report highlighting activities and materials developed throughout the Region was produced in English and Russian <http://www.euro.who.int/en/health-topics/disease->

[prevention/vaccines-and-immunization/publications/2016/european-immunization-week-2016-narrative-report](#)

Support for online communication about immunization

To maintain public trust in and support for immunization, it is essential that accurate and reliable information on immunization is available and easily accessible to the public online in national languages.

WHO-IDEA therefore continues to support countries in addressing this need. IDEA contributes to WHO headquarters' Vaccine Safety Net (VSN) as a member of the VSN advisory group. One of the main objectives is to expand the list of WHO-approved websites on immunization to include sites in Russian and other European Region languages not yet represented, as well as pro-immunization social media accounts. Desk research has identified websites and social media accounts maintained in the Russian language that could potentially apply for inclusion in the list, and contact has been initiated with managers/owners of several of these sites.

A first-ever meeting of VSN members was organized by the VSN advisory group and secretariat in November 2016. Collaboration will continue in 2017 to develop networking opportunities for VSN members by means of a new online portal, a unique data-sharing project that will enable analysis of global data and signalling of online trends, and a package of tools for potential members, including further development of the expanded website template and social media guidance initiated by WHO-IDEA.

WHO-IDEA will continue to explore further opportunities to support countries in this area, for example by including these topics in communication reviews, capacity-building workshops and EIW support.

Networking in the immunization community



immunize-europe.org

A project to investigate and assess the feasibility of establishing and maintaining a web-based collaboration and knowledge-sharing platform for immunization managers and teams, and/or a public forum for the entire immunization community in the European Region was conducted in November 2015. The research included investigation of available platforms, a survey of potential users and in-depth interviews with main stakeholders to identify needs and requirements.

Based on the findings, the Immunize Europe Forum (www.immunize-europe.org) was developed and launched in April 2016. The Forum is a year-round space for sharing and discussion that replaces the previous EIW forum, whose members were automatically migrated to the new site. WHO/Europe manages the Forum and provides regular inputs in the form of new visuals, themes and links, as well as regular email updates to members. But the majority of content and the future of the site are in the hands of its members. Content in the first nine months focused on EIW events and materials, the OPV switch, data visualization, education on immunization, the role and importance of NITAGs and the Influenza Awareness Campaign. The Forum is also being used as a closed place for further collaboration among participants of a meeting for German-speaking NVCs conducted in Innsbruck, Austria in January 2017. In its first nine months, the Forum attracted over 4000 unique visitors and

21,000 page views. Peaks in traffic were experienced in relation to EIW and the Flu Awareness Campaign.

A second part of this networking project is to design and launch a closed space where immunization programme managers can exchange resources and ideas securely and efficiently. Sharepoint has been chosen as the best platform for this purpose, and a dedicated site is being developed that will meet the managers' needs as well as those of VPI in maintaining the network and in providing information and resources to its members. Launch of this site is projected for Q1 in 2017.

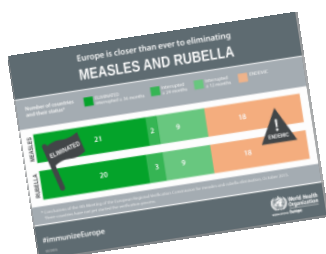
Public seminar on measles and rubella elimination

VPI collaborated with the London School of Hygiene & Tropical Medicine to organize a full-day expert seminar on 20 September 2016 whose objectives were to show how far the European Region has come and what remains to be done to achieve regional elimination; examine how some countries have overcome barriers to elimination and how others may learn from these strategies; review recent advances in our understanding of measles elimination, attitudes towards vaccination and accurate measurement of vaccine safety.

Experts in disease control, health policy, epidemiology, behavioural science and the media shared their experiences and discussed the way forward during a full day of presentations and a panel discussion. Based on these discussions and interviews with key participants conducted in parallel, a video (in English and Russian) with key messages to policy-makers is being developed and will be launched together with the 2016 report of the Regional Verification Commission for measles and rubella elimination on 30 January 2017. The audio material is also being used to develop a podcast on measles and rubella elimination to be launched during EIW 2017.

It is envisioned that this event will become the first in a series of annual public meetings on priority topics.

Ensuring a regional platform for promotion of immunization



Measles and rubella elimination target advocacy

With the second target date for measles and rubella (MR) elimination passed by the end of 2015, advocacy and messaging is critical to maintain awareness, interest and momentum in the Region. This is particularly important since this target was met by some countries – but not all.



WHO-IDEA has developed an advocacy and communications strategy for the MR elimination target defining messaging and stipulating a range of advocacy activities, including a symposium and debate at the London School of Hygiene and Tropical Medicine, **United Kingdom**, on 20 September 2016 (see above).

The key messages are further supported by information products including infographics, banners and news stories on the EURO website. A press release announcing progress towards measles and rubella elimination based on the conclusions of the 2015 RVC meeting was launched upon publication of the meeting report in April 2016. Measles and rubella elimination was also the main focus of European Immunization Week 2016 (see above).

European Vaccine Action Plan (EVAP) promotion



VPI's 2015 annual report *Immunization Highlights* (in English and Russian:

<http://www.euro.who.int/en/health-topics/communicable-diseases/poliomyelitis/publications/2016/immunization-highlights-2015>)

illustrates how the programme's activities and priorities correspond to the EVAP objectives set by the Member States. The 2016 annual report will be combined with a mid-term EVAP progress review and launched in Q2 2017.

A mapping illustration showing how EVAP's goals and objectives align with and contribute to Agenda 2030's Sustainable Development Goals (SDGs) is being developed and will soon be posted on the EURO intranet site as part of a toolkit on the SDGs.

Publications and reports

WHO-IDEA also facilitated the finalization, editing, layout and online posting of all technical meeting reports, including ETAGE, RCC and RVC annual reports. Support was also provided for publication of a Russian language version of a book on biosecurity produced by the Danish Centre for Biosecurity and Biopreparedness.

WHO-IDEA is continuously expanding a library of approved images for use in publications and VPI web pages. In 2016, a professional photographer documented EIW activities and the measles outbreak and response in Romania, thereby filling important gaps in the Regional Office's corporate image library.

Website

WHO/Europe's website and social media accounts are important channels through which VPI informs the public and other stakeholders about vaccine-preventable diseases, immunization-related developments in the Region, WHO guidance and recommendations and other aspects of VPI work.

The web pages of the VPI programme are well visited, with over 100,000 page views to the "Vaccines and immunization" (V&I) site and over 50,000 page views to the disease-specific sites in 2016. The V&I site continues to be among the most visited health topics on the WHO/Europe website.



Maintaining and improving the website is a continuous process. Over 25 news items and other new content were produced by WHO-IDEA in 2016, including the regular posting of information on the Ukraine polio outbreak and response activities. In addition, several improvements were made, including consolidation of pages for better navigation, replacement of images, creation of a standalone EIW event subsite for 2016, restructuring of the publications section, expansion of information and resources on POSE exercises, TIP projects, the OPV switch and poliovirus containment. As the most important reflection of VPI's work, the publication pages of all subsites were translated and made available in Russian (<http://www.euro.who.int/ru/health-topics/disease-prevention/vaccines-and-immunization/publications>). The ongoing revision process is informed through consultations with VPI team members, the WHO/Europe web team and an external user experience review.

Social media

The VPI twitter account (@WHO_EUROPE_VPI) continues to grow in reach and followers. Engagement with influential individuals, organizations and professional associations significantly increases the number of people receiving our messages. Twitter is especially effective in spreading positive messages and directing traffic to publications, features and news on our websites, posts on the Immunize Europe Forum and to useful external news and resources. While the account is maintained throughout the year, peak activity takes place during events of special importance to VPI, including EIW, World Hepatitis and World Polio Days and the Regional Committee Meeting. A social media package distributed to Member States prior to EIW 2016 included sample posts for Facebook and Instagram, which were translated into several European languages. This package contributed to unprecedented visibility on social media for the campaign. For example, in April 2016, over 7000 tweets containing the #EIW2016 hashtag were sent or retweeted by over 3000 contributors. The EIW messages reached the accounts of over 6 million twitter users. Tweets in Spanish were especially popular.



Further outreach

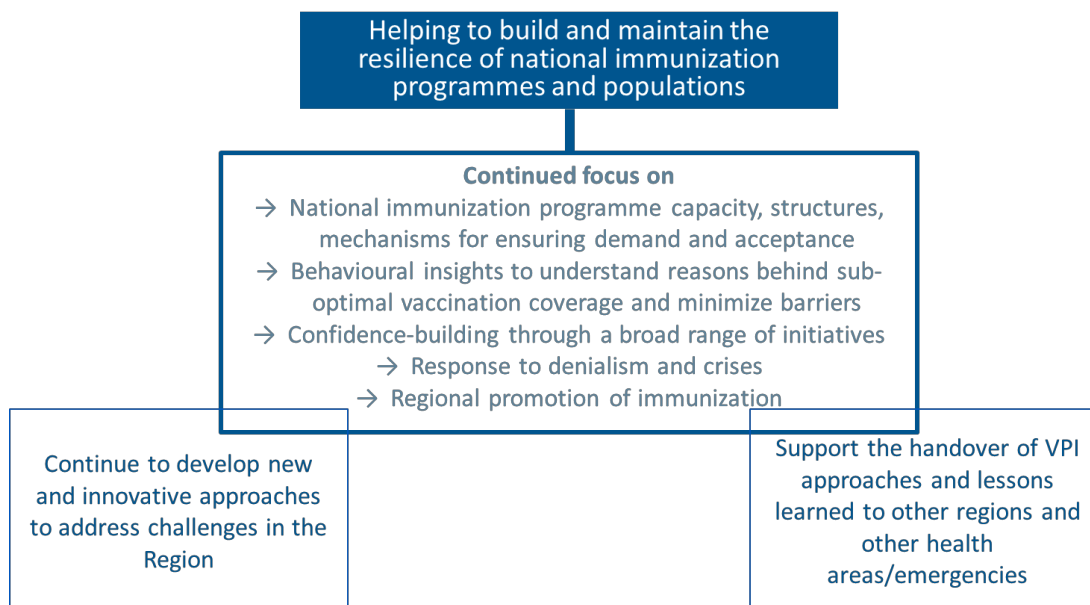
WHO-IDEA contributes regularly to the WHO Global Immunization Newsletter, which is available online and disseminated to WHO's global network (<http://www.who.int/immunization/gin/en/>).

Updates on VPI publications and important announcements are sent regularly to the VPI email network, which includes approximately 900 immunization stakeholders. This resource has been improved through clean-up and migration to the mailchimp platform, which facilitates better maintenance and enables recipients the opportunity to subscribe or unsubscribe to the list.

Continued work in 2017

Responding to requests for support from Member States and the challenges in the Region, WHO-IDEA will continue to develop new approaches, tools and guidance within the priority areas, while at the same time further refining and disseminating existing tools and support mechanisms.

Fig. 3: WHO-IDEA focus in 2017



Promoting WHO/Europe tools and approaches in other regions

Based on lessons learnt in the European Region, WHO-IDEA will scale up the handover of successful tools and approaches to other regions, including low-income settings and to other health areas, including emergencies. Areas where WHO headquarters are planning to adopt or adapt EURO tools and approaches for global use include:

- TIP behavioural insights approach
- Confidence-building and crisis response package
- Guidance on responding to vocal vaccine deniers
- HPV introduction and crisis response package
- Template and guidance for national immunization websites
- Immunization communication review methodology

WHO-IDEA will work together with WHO headquarters and other WHO regional offices to ensure the necessary transfer of knowledge, including through participation in the planning and facilitation of a planned sub-regional training workshop on vaccine confidence-building and crisis response in the Western Pacific Region in March 2017, through a global TIP workshop expected to take place in Q1 2017, and through WHO-IDEA's active participation in the global Vaccine Safety Network.

FIFTH HEPATITIS B IMMUNIZATION EXPERT RESOURCE PANEL CONSULTATION, 15–17 FEBRUARY 2017, MANILA, PHILIPPINES

The hepatitis B Expert Resource Panel (ERP) was created in 2007 to support efforts to reach the hepatitis B control goal in the Western Pacific Region. The ERP advises on hepatitis B control status, supports the verification process and serves on Member State verification panels. Much progress has been made in hepatitis B control in the Region, including the achievement of the 2012 milestone of reducing chronic infection prevalence in children to less than 2%. Additional guidance is needed to sustain these achievements, reach the less than 1% goal and improve performance in priority countries.

The fifth ERP meeting was attended by representatives from six countries in the Western Pacific Region who participated in the 2015 Consultation on Improving and Monitoring Hepatitis B Birth Dose Vaccination. The participants presented their country's progress in implementing the meeting's recommendations and discussed their near- and long-term planned hepatitis B (HepB) birth dose (BD) activities. WHO staff from headquarters, Western Pacific Region, South-East Asia Region and European Region presented updates on regional and global activities. An U.S. Centers for Disease Control and Prevention (CDC) presented on HepB impact serosurveys and outside-the-cold-chain (OCC) pilot projects that were implemented in the Region. It was generally recognized that the Western Pacific Region leads the way in responding to HepB elimination goals through the widespread scale-up of HepB immunization, in particular, use of HepB-BD throughout most of the countries and areas in the Region.

Objectives

The Fifth Hepatitis B Immunization Expert Resource Panel Consultation was held in Manila, Philippines from 15 to 17 February 2017. The objectives of the consultation were:

- to review the verification status by country and provide country-specific recommendations, as necessary;
- to review and provide guidance on progress made in national action plans developed during the 2015 Consultation on Improving and Monitoring HepB Birth Dose Vaccination, which involved six priority countries with low BD coverage; and
- to provide guidance and review immunization targets developed in the new *Regional Action Plan for Viral Hepatitis in the Western Pacific 2016–2020* and the *Global Health Sector Strategy for Viral Hepatitis 2016–2021* (GHHSVH).

Conclusions

- The ERP is extremely pleased by the report in the May 2016 Vaccine publication that the 2017 seroprevalence target of 1% among immunized cohorts of children

at least 5 years of age was met and immunization programmes in this region have averted an estimated 7 million deaths and 37.6 million chronic HepB cases among children born between 1990 and 2014.

- The ERP discussed developing post-2017 HepB control targets for the Western Pacific Region, recognizing the disparity between countries and areas that continue to meet new regional targets and those with relatively low HepB-BD and three dose (HepB3) coverage that have not yet met the 2013 or 2017 targets. Of the 36 countries and areas in the Western Pacific Region, 19 countries have serosurvey evidence of having less than 0.5% hepatitis B surface antigen (HBsAg) prevalence among 5-year-olds; two countries are between 0.5% and 1%; five countries are above 1%, with four of these above 2%; and 10 remaining countries do not have serosurvey results. Post-2017 targets tentatively include the following:
 - 1) all countries and areas in the Western Pacific will reduce HBsAg prevalence to less than 1% among 5-year-old children by 2025; and
 - 2) countries and areas in the Western Pacific that have reduced HBsAg prevalence to less than 1% among 5-year-old children will aim to further reduce HBsAg seroprevalence to less than 0.5% among 5-year-old children by 2025.

Concerted effort and direct assistance will likely be necessary to assist countries and areas that have not reached the 2013 and/or 2017 prevalence goals. These efforts are ultimately geared towards reaching the GHHSVH goal of eliminating viral hepatitis as a public health threat through the adoption of a global target of 0.1% by 2030.

- The ERP recommends that efforts to eliminate HepB infection should not be conducted in a vertical programme. Linking with other programmes, such as elimination of mother-to-child transmission (EMTCT) efforts for HIV and syphilis, other Expanded Programme on Immunization (EPI) programmes and maternal, newborn and child health (MNCH) programmes among others, could help strengthen health systems. Incorporating key health indicators and metrics could prove beneficial in the regional and global movement towards elimination of HepB as a public health threat by 2030.

Recommendations for Member States

1. The ERP reaffirmed the importance of using OCC vaccines in remote and hard-to-reach areas, in regions where inadequate cold chain capacity exists, in countries with a high proportion of home deliveries, and for vaccinating babies born at home, preferably within 24 hours of birth
 - Affirming that countries and areas should dedicate support to improve cold chain capacity, the ERP also endorses the incentive for countries and areas to increase health facility delivery rates, while acknowledging the existence of settings and environments where home births will require OCC vaccines to improve HepB-BD coverage.



2. Discrepancies remain in reaching national 2013 and 2017 vaccination control targets in the Region. The ERP encouraged all countries and areas to continue efforts to improve BD coverage targets in order to eventually reach elimination goals nationally and at the subnational level.
3. The ERP recommended that countries continue to proactively mitigate against negative perceptions of HepB immunization through proactive risk communication planning and health education outreach. The ERP acknowledged the proactive work of Viet Nam in this regard since the previous ERP meeting in Hanoi in January 2016.
4. The ERP affirmed the need for countries and areas to develop health-care worker policies for HepB vaccination. The recommendation is in line with the goal put forth in the *Regional Action Plan for Viral Hepatitis in the Western Pacific*, i.e. a national policy of vaccinating health-care workers against HepB should be established in over 80% of countries by 2017 and in all countries by 2020.
5. The ERP acknowledges the tremendous efforts by high-burden countries to implement national HepB-BD plans developed during the 2015 Consultation on Improving and Monitoring Hepatitis B Birth Dose Vaccination meeting. By countries, the ERP recommends the following actions be taken:

Lao People's Democratic Republic

- The ERP encourages the National Regulatory Authority and Ministry of Health in the Lao People's Democratic Republic to endorse national guidelines including the use of OCC vaccines.
- The ERP commends the Lao People's Democratic Republic on efforts to scale up OCC HepB-BD vaccine, and recommends ongoing reporting on progress and outcomes.
- As previously described, WHO Regional Office for the Western Pacific and headquarters will be assisting the Lao People's Democratic Republic to amend guidelines that contain recommendations for using OCC HepB-BD.
- The ERP recognizes that reaching remote populations is an ongoing challenge in the Lao People's Democratic Republic and commits to working with the country to determine methods to improve HepB-BD coverage in these regions.

Papua New Guinea

- The ERP commends Papua New Guinea on the development of strategies to improve HepB-BD coverage in the country.
- The ERP, WHO Regional Office for the Western Pacific and WHO headquarters will assist in obtaining approvals for using OCC HepB-BD.
- Recognizing the importance of community awareness, the ERP will work with Papua New Guinea to develop effective public awareness campaigns to encourage women to deliver at health facilities and receive timely birth dose.
- The ERP recognizes that reaching remote populations is an ongoing challenge in Papua New Guinea and commits to working with the country to determine methods to improve HepB-BD coverage in these regions.



Viet Nam

- The ERP commends the efforts in Viet Nam to improve HepB-BD coverage.
- The ERP acknowledges the steps that Viet Nam has taken in mitigating against negative publicity about HepB vaccines through programmes such as training of journalists. The ERP suggests that Viet Nam enhance public and health-care worker awareness programmes using a broad range of strategies to provide information about the benefits of the HepB vaccination programme. Materials for improving awareness, how to build resilience, proactive involvement of media, communication with patients, and improving health-care workers' response to vaccine refusals will be shared from the WHO Regional Office for Europe and the CDC.
- The ERP will work with Viet Nam to integrate the aforementioned activities with MNCH efforts to encourage more facility deliveries.
- The ERP will continue to assist Viet Nam with plans to reach populations in remote areas, including strategies to use OCC HepB-BD.
- The ERP urges Viet Nam to include standing orders to administer HepB-BD and to remove the neonatal screening form 2301/QD-BYT, which erroneously precludes neonates from receiving a HepB-BD by listing false contraindications and forcing a physician to sign this form before HepB-BD can be administered.
- The ERP commends current efforts in Yên Bái province to expand HepB-BD coverage among polyclinics and commune health clinics to other districts and scale up to other provinces with low HepB-BD coverage, prioritizing: 1) polyclinics that have proper cold chain monitoring in place; and 2) commune health clinics with high delivery rates.

Cambodia

- The ERP congratulates Cambodia on successfully increasing their HepB-BD and HepB3 coverage over the past 5 years.
- The ERP will support Cambodia's planned programmatic activities to sustain successful outcomes, including conducting their first nationally representative HepB serosurvey in 2017.

Philippines

- The ERP acknowledges some of the steps taken by the Philippines to try to improve HepB-BD coverage, including the recent change to use UNICEF to procure HepB3 and thereby avoid HepB3 stock outs that have been a factor in persistently low HepB3 coverage in recent years.
- The ERP recommends the Philippines focus on improving timely birth dose coverage among all health facility births.



- The ERP commends and supports the Philippines on the imminent implementation of a HepB seroprevalence survey in children 5 years old and above in late 2017/early 2018.
- The ERP recommends the Philippines intensify integrated field monitoring in coordination with the MNCH programme in priority areas.
- The ERP will support the Philippines Government to scale up HepB-BD and routine immunization by sharing materials targeting the public and health-care workers on the importance of HepB-BD vaccination in preventing liver cancer and cirrhosis.

Solomon Islands

- The ERP supports Solomon Islands in attempts to scale up OCC HepB-BD in a phased manner.
- The ERP commends efforts to raise awareness and create a demand for immunization by the public.
- The ERP, WHO Regional Office for the Western Pacific and headquarters will assist in the efforts to obtain approvals for using OCC HepB vaccine.
- The ERP recognizes that reaching remote populations is an ongoing access challenge in Solomon Islands and commits to working with the country to determine methods to vaccinate children in these hard-to-reach regions.

Japan

- The ERP commends Japan's recent introduction of hepatitis B vaccination into their routine immunization programme at 2, 3 and 7–8 months after birth. This inclusion was based on well-researched findings that showed hepatitis B core (HBc) antibody seroprevalence among teenagers was higher than HBsAg prevalence among immunized younger child populations, suggesting that horizontal transmission was a potential source for transmission.
- The ERP recommends continuation and evaluation of the HBsAg screening programme to ensure all pregnant women are screened and all children of HBsAg-positive mothers are given their BD and Hepatitis B immune globulin (HBIG) treatment.
- With an estimated hepatitis B prevalence among children of 0.03% (9 out of 27 240), Japan should consider submitting their application for verification of meeting the regional 2017 target of 1%.

New Zealand

- The ERP recommends New Zealand to implement a universal HepB immunization programme including BD for all infants.
- Given the increasing number of migrant populations and foreign-born women of childbearing age, discussions with New Zealand's National Immunization Technical Advisory Group (NITAG) and Ministry of Health should be performed to ascertain whether timely birth dose could be universally provided to all newborns.



Recommendations for WHO Secretariat

1. With the Strategic Advisory Group of Experts (SAGE) strongly urging manufacturers of monovalent HepB vaccine to pursue regulatory approval for controlled temperature chain (CTC) as soon as possible, the ERP urges WHO headquarters and UNICEF to do the following:
 - Support countries seeking regulatory approval for using OCC HepB vaccine.
 - A. The Western Pacific Region has extensive experience in conducting successful OCC pilots in China, Cambodia, the Lao People's Democratic Republic, Papua New Guinea and Solomon Islands. To date, none of these projects has been scaled up nationally. The ERP recommends that the WHO Regional Office monitor the interest and ability of countries and areas to scale up successful OCC pilots, starting with potential consideration to assisting the Lao People's Democratic Republic. The WHO Regional Office should explore the mechanisms and capacity to obtain OCC regulatory approval in key countries interested in using OCC vaccines. The lessons learnt on OCC scale up barriers and possible solutions should be shared with headquarters and among countries that may have fully functional regulatory bodies.
 - B. WHO headquarters should draft reports synthesizing findings and conclusions of available thermostability data for HepB vaccines that could be used outside the cold chain, including suggested peak temperatures and the number of days at maximum temperature. The purpose of these product-specific reports would be to serve as a resource for EPI programmes, regulatory authorities and NITAGs.
 - Perform actions related to manufactures.
 - A. Based on prior experience with UNICEF only procuring vaccines with vaccine vial monitors (VVMs), WHO headquarters and UNICEF should explore the potential for preferential procurement of WHO pre-qualified monovalent HepB vaccines that have been relabelled for CTC use by manufacturers, including vaccines presented in compact pre-filled non-reusable injection devices.
 - B. In relation to the ERP's concern that manufacturers may not be incentivized to take the steps required for CTC pre-qualification, WHO headquarters should communicate with the WHO Regional Office if manufacturers require data or information on programme demand for a pre-qualified CTC product.
 - C. WHO headquarters should contact manufacturers of vaccine in compact pre-filled non-reusable injection devices to explore the product availability and cost.
 - D. WHO headquarters should investigate opportunities for GAVI to support manufacturers with costs related to CTC pre-qualification and market shaping for affordable CTC vaccines.
2. The ERP encourages the Western Pacific Region to gain experience in using new methods to measure low HBsAg prevalence targets, including: classification serosurveys, which are based on the updated WHO vaccination cluster survey guidelines; a two-step risk assessment and verification serosurvey method that has been used for verification of neonatal tetanus elimination; and HepB serosurveys incorporated into other national coverage surveys such as DHS or MICS or potentially other HIV/AIDS and malaria serosurveys.
3. The ERP affirms the need for WHO to conduct cost-effectiveness analyses and incremental cost-effectiveness ratios to help countries and areas ascertain which potential interventions,

including multiple interventions, are programmatically and financially feasible. In addition to the cost-effective inclusion of HepB-BD, potential intervention options include universal antenatal screening (including HBeAg screening), antiviral therapy (including the threshold to commence treatment) and HBIG treatment and post-vaccination serological testing among children born to HBsAg-positive mothers.

4. The ERP recommends that public awareness campaigns directly linking hepatitis B transmission in infancy to potentially developing liver cancer or cirrhosis later in life may motivate parents to have their infants vaccinated at birth and during routine immunizations. Communication and advocacy activities are needed to draw public attention to HepB and its consequences. WHO could mobilize the resources, by collaborating with nongovernmental organizations and academic institutions, to assist with translating evidence into best practices. Traditional and social media, celebrity engagement and visits by high-ranking officials are all methods to be considered in raising public awareness about HepB vaccination.
5. WHO should regularly disseminate reports reviewing progress towards targets. Countries and areas in the Western Pacific Region should be made aware of their achievements as well as areas for improvement. Annual reports, meetings and teleconferences could be held to share information.



Update on the Gavi Board meeting 2-3 December 2016

Overall, there is early progress on implementation of 2016-2020 strategy, but significant challenges and risks remain including coverage and equity, sustained transitioning of countries, country partner and ministry of health staff capacity, and expectations on HPV and yellow fever to further increase Gavi's impact.

The CEO of the Alliance, highlighted that due to the IPV supply situation Gavi will likely be faced for the first time with the situation to have to stop providing vaccine introductions. The CEO referred to some of the challenges Gavi is facing in the context of a changing global landscape with a number of recent and potential future changes in leadership among key donors and partners, as well as in implementing countries. He welcomed the positive outcome for Gavi of the Department for International Development (DFID) Multilateral Development Review 2016 and provided information in relation to the intensification of engagement with new and potential new donors. He reminded Board members that vaccines have been included in two health targets of the Sustainable Development Goals (SDG) and that two indicators have also been accepted, but which are pending endorsement by the United Nations Stats Commission in March 2017.

The CEO referred to the ever increasing global health threats and the growing risk factors such as climate change, population growth, urbanisation and migration, citing the examples of recent Zika and Yellow Fever outbreaks. He also highlighted recent setbacks to polio eradication as well as challenges relating to antimicrobial resistance.

Key decisions made by the Board include:

- Approved funding for an aggregated amount not exceeding USD 250M for existing and new Cold Chain Equipment Optimisation Platform (CCEOP) programmes;
- Approved support for the immunisation of children in Syria, an annual amount of up to USD 25M for 2017-2018 for procuring vaccines and cold chain equipment through UNICEF;
- Approved additional funding for HPV vaccine countries of up to USD72M for 2016-2108, including national introduction and to support multi-age vaccinations in line with our recent SAGE recommendations.

The Board highlighted the “blurredness” in relation to the continued resistant for Gavi to have an observer status on the International Coordinating Group (ICG) managing emergency vaccine stockpiles which includes four member organisations: International Federation of Red Cross and Red Crescent Societies (IFRC); Medecins Sans Frontieres (MSF); UNICEF; and WHO which also supports the Secretariat of the ICG. The Board further noted that the ICG evaluation is not seen as a way out and may not lead to desired outcomes for all when it is eventually completed. The Board Chair requested the Board's decision and “mood” on this issue, be conveyed to the senior managements of ICG member organizations.

Concerns were also raised by the Board in terms of governance and fragmentation with emerging organisations with similar mandates becoming an issue for industry and for developing countries (Gavi, CEPI, GPEI, WHE, Global Fund). Suggestions were made for mapping all the partnerships and organisations engaged in immunization.

Recommendations from the Governance and Board self-evaluation processes will be deliberated on during the 4-5 April 2017 Board retreat .



Contents

- 13 Global Advisory Committee on Vaccine Safety, 30 November – 1 December 2016

Sommaire

- 13 Comité consultatif mondial pour la sécurité des vaccins, 30 novembre - 1^{er} décembre 2016

Global Advisory Committee on Vaccine Safety, 30 November – 1 December 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 35th meeting in Geneva, Switzerland, on 30 November and 1 December 2016.² The Committee examined 2 generic issues: updates on its operations following a review conducted in 2014, and progress with developing the Vaccine Safety Net. It also reviewed vaccine-specific safety issues concerning typhoid vaccines, yellow fever vaccines and new data examining the relationship between the occurrence of narcolepsy and administration of p2009H1N1 monovalent vaccines.

Vaccine Safety Net

The Vaccine Safety Net (VSN) is a WHO initiative supported by GACVS that recognizes websites providing information on vaccine safety and immunization as meeting quality and content standards. The objective of the VSN is to facilitate access for public health authorities, health professionals and the public to reliable information on vaccine safety via the Internet. There are currently 46 member websites in 11 languages, covering 5 WHO regions. Two sites from the WHO Eastern Mediterranean Region are under review. After more than 10 years of remote collabora-

Comité consultatif mondial pour la sécurité des vaccins, 30 novembre - 1^{er} décembre 2016

Le Comité consultatif mondial pour 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 35^e réunion à Genève (Suisse) les 30 novembre et 1^{er} décembre 2016.² Il a abordé 2 questions génériques, avec une mise à jour sur ses activités suite à une analyse réalisée en 2014 et un aperçu des progrès accomplis dans la mise en place du Réseau pour la sécurité des vaccins. Il a également examiné des questions de sécurité spécifiques, portant sur les vaccins antityphoïdiques, les vaccins anti-amarils et les nouvelles données concernant le lien entre les manifestations de narcolepsie et l'administration des vaccins monovalents contre les virus grippaux p2009H1N1.

Réseau pour la sécurité des vaccins

Le Réseau pour la sécurité des vaccins (VSN) est une initiative de l'OMS, appuyée par le GACVS, qui consiste à reconnaître, parmi les sites Web qui fournissent des informations sur la vaccination et la sécurité des vaccins, ceux qui répondent à des normes de qualité et de contenu. L'objectif du VSN est de faciliter l'accès des autorités de santé publique, des professionnels de la santé et du public à des informations fiables sur la sécurité des vaccins sur Internet. Le réseau compte actuellement 46 sites Web dans 11 langues différentes, couvrant 5 Régions de l'OMS. Deux sites de la Région OMS de la Méditerranée orientale sont

WORLD HEALTH
ORGANIZATION
Geneva

ORGANISATION MONDIALE
DE LA SANTÉ
Genève

Annual subscription / Abonnement annuel
Sw. fr. / Fr. s. 346.–

01.2017
ISSN 0049-8114
Printed in Switzerland

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: University of Maryland School of Medicine, Baltimore MA, USA; University of Ghana Medical School, Accra, Ghana; US Centers for Disease Control and Prevention, Atlanta GA, USA; Ospedale Pediatrico Bambino Gesù, Rome, Italy; Erasmus University, Rotterdam, The Netherlands; Bharat Biotech International, Hyderabad, India.

¹ Voir N° 41, 1999, pp. 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 notamment de personnes affiliées aux organismes suivants: Faculté de médecine de l'Université du Maryland, Baltimore MA (États-Unis); Faculté de médecine de l'Université du Ghana, Accra (Ghana); Centers for Disease Control and Prevention, Atlanta GA (États-Unis); Ospedale Pediatrico Bambino Gesù, Rome (Italie); Université Erasmus, Rotterdam (Pays-Bas); Bharat Biotech International, Hyderabad (Inde).

tion, VSN members met at WHO headquarters in Geneva on 28–29 November 2016 to review the past decade of their VSN membership, to share their views and experiences and innovations in managing digital communication and vaccine safety information, and to explore new frontiers in the gathering of this information. In addition, members expressed their expectations for the future of the network, presented tools to enhance the cohesiveness, communication and collaboration between members, and planned next steps. A report and outcomes of the meeting were presented to GACVS. The meeting convened 25 representatives of VSN sites, joined by others via videoconference, to conduct a situation analysis and explore new initiatives. A survey of VSN member websites in 2015 revealed strong interest for members to maintain better contact through mechanisms such as a VSN portal, workshops and improved links to WHO.

During the 2-day meeting, participants were presented with a unique project on how to use web analytics to support more effective vaccine safety information on the Internet. There are currently no standards and no evidence supporting such activity or this project. Sharing anonymized data on website analytics (such as number of visitors, what countries they come from, and what information they seek) and analysing the data, may improve the network and help members improve their own sites. While each website is unique, supporting consistency of information across VSN websites can assist global information campaigns such as during world immunization week.

Outcomes of the meeting included strengthened links between members who had exchanged best practices, challenges and new opportunities with advances in web communication. In addition, members reinforced the current VSN mission and objectives and began the process of defining a vision and goals and establishing an advisory group. The new VSN portal will be launched later in January 2017 and members will integrate a newly-approved visual identity icon on their websites, indicating that they have met the revised criteria for quality and content endorsed by GACVS. Most members agreed, in principle, to participate in a web analytics project.

GACVS seeks to improve its communication of vaccine safety information to the public as well as its partners; it welcomes the contribution of the VSN in these efforts and will be following developments closely. In the current overloaded web communication environment, where information competes for attention, easy access to reliable and trustworthy content on immunization is paramount.

en cours d'évaluation. Après plus d'une décennie de collaboration à distance, les membres du VSN se sont réunis au Siège de l'OMS à Genève les 28 et 29 novembre 2016 pour dresser le bilan de leur participation au réseau au cours des 10 dernières années, procéder à un échange de points de vue, d'expériences et d'innovations concernant la gestion de l'information et des communications numériques sur la sécurité des vaccins, explorer de nouvelles perspectives en matière de collecte d'information sur la sécurité des vaccins. D'autre part, les membres ont exprimé leurs attentes quant à l'avenir du réseau, présenté des outils susceptibles d'améliorer la cohésion, la communication et la collaboration entre les membres et planifié les prochaines étapes. Un compte-rendu de cette réunion et de ses résultats a été présenté au GACVS. Vingt-cinq représentants de sites membres du VSN ont participé en personne à cette réunion, avec d'autres membres se joignant aux débats par vidéoconférence, pour échanger leurs perspectives et leurs expériences, mener une analyse de la situation et explorer de nouvelles initiatives. Une enquête menée auprès des sites Web membres du VSN en 2015 a mis en évidence le vif désir des membres d'entretenir des contacts plus étroits entre eux, au moyen de mécanismes tels que des portails et des ateliers, et de renforcer leurs liens avec l'OMS.

Durant cette réunion de 2 jours, les participants ont pris connaissance d'un projet inédit d'utilisation des données d'analyse d'audience Web pour accroître l'efficacité de la communication sur la sécurité des vaccins sur Internet. Il n'existe actuellement aucune norme et aucun élément d'appréciation à l'appui de cette activité et de ce projet. Le partage de données anonymes d'analyse d'audience des sites Web (comme le nombre de visiteurs, les pays d'où ils viennent, le type d'information recherchée, etc.) et l'analyse de ces données pourraient non seulement contribuer à renforcer le réseau, mais aussi aider les membres à améliorer leur site individuel. Bien que chaque site soit différent, la cohérence de l'information entre les sites membres du VSN peut faciliter les campagnes mondiales d'information, notamment durant la semaine mondiale de la vaccination.

Cette réunion a abouti à un renforcement des liens entre les membres du réseau ayant participé à cet échange sur les meilleures pratiques, les difficultés rencontrées et les nouvelles possibilités offertes par les avancées en matière de communication sur Internet. Les membres ont en outre conforté la mission et les objectifs actuels du VSN et ont amorcé le travail de définition de la vision et des buts du réseau, ainsi que l'établissement d'un groupe consultatif. Le nouveau portail du VSN sera mis en ligne en janvier et les membres afficheront une nouvelle icône d'identité visuelle sur leur site Web, indiquant qu'ils satisfont aux critères révisés de qualité et de contenu approuvés par le GACVS. La plupart des membres ont accepté en principe de participer au projet sur les données d'analyse d'audience Web.

Souhaitant améliorer la manière dont il communique les informations relatives à la sécurité des vaccins au public et à ses partenaires, le GACVS se félicite de la contribution apportée par le VSN à ces efforts et suivra de près l'évolution de ce réseau. Dans l'environnement de communication Web actuel, caractérisé par une surcharge d'informations qui se font concurrence pour attirer l'attention du public, il est primordial de garantir un accès aisé à des contenus fiables et crédibles en matière de vaccination.

Update on GACVS operations

The Global Advisory Committee on Vaccine Safety is mandated to conduct risk-benefit assessment for immunization policies and procedures under consideration by WHO Member States and the Strategic Advisory Group of Experts (SAGE). In 2014, a review was conducted by current and former members of GACVS³ to assess the role of the Committee on immunization policy and its impact on global vaccine safety. The review included a quantitative and qualitative examination of contributions and explored the extent to which GACVS has been influential. Future challenges of GACVS and its mandate were also considered.

The 2014 review documented the productivity and influence of GACVS in supporting global safety efforts, including the publication of more than 100 reports, as well as statements and guidelines issued to inform public policies and respond to safety concerns. Challenges identified included the, often limited, evidence available for scientific assessment, along with difficulties in requesting further research on a specific topic, the need to incorporate review systems, such as GRADE – aimed at assessing intervention effectiveness but not always well suited to post-marketing vaccine safety questions (which usually require consideration of valuable post-licensure data) – and the challenge to support countries with more limited capacity to identify and assess safety signals. Moreover, the confidentiality of some of the evidence presented to GACVS and the need for enhanced transparency of processes presented additional challenges in the reporting of its work. A survey conducted in preparation of the review suggested that the audience of GACVS needs to be better articulated and defined, thus highlighting the need for a defined communications strategy. This is particularly exemplified by safety concerns that have been resolved at the scientific and policy levels, but still require public communication since many stakeholders may not have been sufficiently informed of the available evidence.

In discussing the recommendations, the Committee focused on 3 key areas: i) the need to apply a more formal systematic review methodology to the work of GACVS; ii) the need to direct more attention to the dissemination of GACVS products to the regulators, programme managers and policy-makers of low- and middle-income countries; and iii) the role of GACVS as an advocate and facilitator in bridging gaps in vaccine safety capacity globally.

The Committee discussed key areas for enhancing the review process. These included the mechanisms and resources required to strengthen the evidence-based approach for the work of GACVS, the need to improve

Le point sur les activités du GACVS

Le Comité consultatif mondial pour la sécurité des vaccins est chargé d'analyser le rapport risque/bénéfice des politiques et procédures de vaccination envisagées par les États Membres de l'OMS et le Groupe stratégique consultatif d'experts (SAGE). En 2014, une analyse a été réalisée en collaboration avec les membres actuels et passés du GACVS³ afin de dresser un bilan objectif du rôle joué par le GACVS dans la politique vaccinale et de son incidence dans le domaine de la sécurité des vaccins dans le monde. Cette analyse comprenait un examen quantitatif et qualitatif des contributions du GACVS pour évaluer l'influence qu'il avait exercée. Elle portait également sur les défis que le GACVS devra relever à l'avenir, ainsi que sur son mandat.

Cette analyse de 2014 a montré que le GACVS a apporté une contribution efficace et influente aux efforts déployés à l'échelle mondiale en matière de sécurité, publiant plus de 100 rapports, ainsi que des déclarations et orientations, pour guider l'élaboration des politiques publiques et répondre aux préoccupations liées à la sécurité. L'analyse a également mis en évidence certains écueils, notamment la disponibilité souvent limitée des données nécessaires à une évaluation scientifique; la difficulté à demander la conduite de travaux de recherche supplémentaires sur un sujet particulier; la nécessité d'incorporer des systèmes d'examen comme GRADE, qui visent à évaluer l'efficacité des interventions et ne sont pas toujours adaptés à l'étude de la sécurité des vaccins après la mise sur le marché (une étude qui exige généralement des données cruciales post-homologation); et la difficulté à soutenir les pays ayant des capacités plus limitées d'identification et d'évaluation des signaux de sécurité. En outre, la confidentialité de certaines données transmises au GACVS, conjuguée à la nécessité d'améliorer la transparence des procédures, font qu'il est parfois difficile pour le GACVS de rendre compte de son travail. Une enquête préalable réalisée dans la perspective de cette analyse a indiqué que le public cible du GACVS gagnerait à être plus clairement défini, faisant ressortir la nécessité d'élaborer une stratégie précise de communication. Ce besoin est en particulier illustré par certaines préoccupations liées à la sécurité qui ont pu être résolues aux niveaux scientifique et politique, mais qui exigent encore un effort de communication publique, de nombreuses parties prenantes n'ayant pas toujours été suffisamment informées des données disponibles.

Le Comité a examiné les recommandations formulées dans le rapport, axées sur 3 domaines clés: 1) la nécessité d'appliquer une méthodologie d'examen systématique plus formelle aux travaux du GACVS; 2) l'attention accrue devant être portée à la diffusion des produits du GACVS auprès des autorités réglementaires, des administrateurs de programmes et des décideurs des pays à revenu faible ou intermédiaire; et 3) le rôle de défenseur et de facilitateur devant être joué par le GACVS pour combler les déficits de capacité en matière de sécurité des vaccins à l'échelle mondiale.

Pour améliorer le processus d'examen, plusieurs domaines clés ont été abordés, notamment les mécanismes et les ressources nécessaires pour renforcer l'approche fondée sur des données probantes employée par le GACVS, la nécessité d'améliorer la

³ Asturias EJ, et al. Contributions and challenges for worldwide vaccine safety: The Global Advisory Committee on Vaccine Safety at 15 years. *Vaccine* (2016), <http://dx.doi.org/10.1016/j.vaccine.2016.05.018>

³ Asturias EJ, et al. Contributions and challenges for worldwide vaccine safety: The Global Advisory Committee on Vaccine Safety at 15 years. *Vaccine* (2016), <http://dx.doi.org/10.1016/j.vaccine.2016.05.018>

the quality of evidence presented to the Committee, and improvements in how the methodology and outcomes can be developed (including increased capacity in low- and middle-income countries), presented and published. Transparency would be enhanced without compromising proprietary information or unpublished work. For example, access to unpublished and confidential reviews performed by regulatory agencies and/or national immunization technical advisory committees (NITAGs), could be requested on a limited basis.

With regard to communications, while meeting reports are published in the *Weekly Epidemiological Record* and made available online, along with statements on the WHO website, there is limited dissemination of the work of GACVS by other means. A mailing list of several thousand members is used; however, two thirds of members are from Europe and the Americas and large audiences from low- and middle-income countries are omitted. The Committee discussed several communication modalities including social media, unknown at the time GACVS was formed.

Finally, GACVS discussed the relationship of its work with the Global Vaccine Safety Initiative (GVSII) which aims to optimize the safety of vaccines through effective use of pharmacovigilance principles and methods, as well as helping to establish more effective safety monitoring in all countries. GACVS is a valuable resource for global vaccine safety and, while GVSII is relatively new, it has become a convening point for low- and middle-income countries and should have greater participation with GACVS. Recommendations included using GVSII to convene Member States to discuss global vaccine safety with GACVS representatives, and to identify priorities at all levels, from local to regional, including facilitating the formation of regional vaccine safety committees and passing urgent and important issues for review by GACVS. Advocacy by GACVS for GVSII activities could also be increased, to include, for example, GVSII helping to address some of the challenges identified by GACVS – GVSII being “closer” to the various players (that include not only countries, but also donor agencies and development partners).

Moving forward, GACVS will continue to explore advanced review methods, examine ways to improve communication of its products, and increase collaboration and capacity-building globally with a focus on low- and middle-income countries.

New data on narcolepsy following the 2009 pandemic influenza vaccine

The Committee was presented with an update of research on the association of adjuvanted p2009H1N1 influenza vaccines and narcolepsy. During the influenza pandemic of 2009, oil-in-water emulsion adjuvants (AS03 and MF59) were used in vaccines to maintain

qualité des données présentées au Comité, et les améliorations à apporter à la manière dont la méthodologie et les résultats sont élaborés (notamment en renforçant les capacités dans les pays à revenu faible ou intermédiaire), présentés et publiés. Cela suppose notamment d'accroître la transparence sans compromettre la confidentialité des informations protégées ou des travaux non encore publiés. Par exemple, seul un accès limité peut être demandé aux analyses non publiées et confidentielles qui ont été réalisées par les organismes de réglementation et/ou les groupes consultatifs techniques nationaux sur la vaccination.

Concernant les communications, bien que des rapports de réunion soient publiés en ligne dans le *Relevé épidémiologique hebdomadaire* et mis à disposition sur le site Web de l'OMS, de pair avec des déclarations spécifiques, l'utilisation d'autres moyens de diffusion pour faire connaître le travail du GACVS reste limitée. Il existe une liste de diffusion comptant plusieurs milliers d'adhérents, mais les deux tiers se trouvent en Europe et aux Amériques – ce qui signifie qu'un vaste public dans les pays à revenu faible ou intermédiaire est omis de cette liste. Le Comité s'est intéressé à plusieurs modalités de communication, notamment celles offertes par les médias sociaux, qui n'existaient pas lorsque le GACVS a été établi.

Enfin, le GACVS a étudié la relation entre ses travaux et ceux de l'Initiative mondiale pour la sécurité des vaccins (GVSII), qui vise à optimiser la sécurité des vaccins par une application efficace des principes et des méthodes de pharmacovigilance et à contribuer à l'établissement d'une surveillance efficace de la sécurité dans tous les pays. Le GACVS apporte une contribution précieuse à la sécurité des vaccins à l'échelle mondiale et l'initiative GVSII, bien que relativement récente, est devenue un point de rencontre pour les pays à revenu faible ou intermédiaire et devrait bénéficier d'une plus grande participation au sein du GACVS. À cet égard, il a notamment été recommandé d'utiliser l'initiative GVSII pour réunir les États Membres et leur permettre de débattre des questions de sécurité des vaccins dans le monde avec les représentants du GACVS, d'identifier les priorités à tous les niveaux – de l'échelon local à régional – en facilitant notamment l'établissement de comités régionaux pour la sécurité des vaccins, et de soumettre des questions urgentes et importantes à l'examen du GACVS. Le GACVS pourrait en outre intensifier son action de plaidoyer en faveur de l'initiative GVSII. Par exemple, la GVSII peut contribuer à relever certains des défis identifiés par le GACVS, grâce à sa plus grande proximité avec les différents acteurs, parmi lesquels figurent non seulement les pays, mais aussi les organismes donateurs et les partenaires de développement.

À l'avenir, le GACVS continuera d'explorer des méthodes d'examen plus avancées, de réfléchir aux moyens d'améliorer la communication de ses produits, et d'œuvrer en faveur d'une plus grande collaboration et d'un renforcement des capacités à l'échelle mondiale, en mettant l'accent sur les pays à revenu faible ou intermédiaire.

Nouvelles données sur la narcolepsie après vaccination contre le virus grippal pandémique de 2009

Le Comité a pris connaissance des dernières études menées sur le lien entre la narcolepsie et les vaccins adjuvants contre le virus grippal p2009H1N1. Durant la pandémie de grippe, des adjuvants d'émulsion d'huile dans l'eau (AS03 et MF59) ont été utilisés pour préserver l'immunogénicité des vaccins lorsque la

immunogenicity when antigen availability was limited and dose sparing was required. As was noted previously by GACVS in the meeting report of December 2015,⁴ there is consistent evidence in Europe of an increased risk of narcolepsy following use of Pandemrix, despite the varying datasets and methods used. New research was presented from a multicountry study sponsored by the United States Centers for Disease Control and Prevention.⁵

The aims of the study were to assess the association of narcolepsy with other adjuvanted vaccines: Arepanrix, an AS03 adjuvanted vaccine used in Canada only, and Focetria, an MF59 adjuvanted vaccine. A small amount of additional data on Pandemrix from the Netherlands was also collected. Adjuvants have been used to produce effective vaccines for the control of many infections, and might be used in future pandemics; hence any evidence to inform their safety profiles is useful. The Committee noted the extensive work required to establish data collection from multiple settings (Canada, Argentina, Taiwan, Netherlands, Spain and Switzerland) to conduct case-control studies as well as to examine time trends in rates of narcolepsy in those and additional settings (Denmark, Sweden and the United Kingdom).

The population-based narcolepsy rates before and after the pandemic were calculated using diagnosed cases from healthcare databases. Provisional analyses suggested little in the way of signals except in Sweden, one of the 2 signalling countries (the other being Finland) where Pandemrix was the only vaccine used and where coverage was high. The recruitment of controls for the case-control studies varied from population-based to hospital-based, depending on the setting, with matching on age, sex and time to cases carried out. Preliminary evidence from the case-control studies was reassuring for Focetria and Arepanrix. For Pandemrix, data were too sparse in this study to draw further conclusions. GACVS is aware that additional data for Pandemrix could be available from several European countries including extended follow-up of published studies that could improve understanding of the association between narcolepsy and Pandemrix. To date, the data presented provide reassurance that, with the exception of the AS03 adjuvanted Pandemrix in several European countries where adolescents and young adults were frequently vaccinated, no other substantial association between the use of p2009H1N1 pandemic virus vaccines and narcolepsy has been identified.

Safety of typhoid vaccines

GACVS was presented with data on the safety of 3 generations of typhoid vaccines, including the live oral

disponibilité des antigènes était limitée et qu'une économie de doses s'imposait. Le GACVS a de nouveau noté l'existence d'indices concordants d'un risque accru de narcolepsie après l'administration du Pandemrix en Europe, malgré la variabilité des ensembles de données et des méthodes employés, comme indiqué dans le rapport de la réunion de décembre 2015 publié dans le *Relevé épidémiologique hebdomadaire*.⁴ Durant la réunion de décembre 2016, le Comité a pris connaissance des nouvelles informations issues d'une étude multipays parrainée par les *Centers for Disease Control and Prevention* des États-Unis d'Amérique.⁵

Cette étude visait à évaluer le lien entre la narcolepsie et d'autres vaccins adjuvés: Arepanrix, un vaccin contenant l'adjuvant AS03 utilisé uniquement au Canada, et Focetria, un vaccin contenant l'adjuvant MF59. Quelques données supplémentaires sur le Pandemrix ont également été recueillies en provenance des Pays-Bas. Des adjuvants ont été utilisés dans la préparation de vaccins efficaces contre de nombreuses infections et sont susceptibles d'être employés pour lutter contre des pandémies à l'avenir. Toute information relative à leur profil de sécurité est donc importante. Le Comité a pris la mesure du travail considérable requis pour établir une collecte des données couvrant plusieurs pays (Argentine, Canada, Espagne, Pays-Bas, Suisse et Taïwan) en vue de mener des études cas-témoins et d'examiner l'évolution dans le temps des taux de narcolepsie, dans ces pays et d'autres (Danemark, Royaume-Uni et Suède).

Les taux de narcolepsie dans la population avant et après la pandémie ont été calculés à partir des cas diagnostiqués contenus dans les bases de données des systèmes de santé. Les analyses provisoires n'ont pratiquement pas révélé de signaux, sauf en Suède, l'un des 2 pays ayant notifié des signaux (l'autre étant la Finlande), où le Pandemrix était le seul vaccin utilisé, avec une forte couverture vaccinale. Le recrutement des témoins pour les études cas-témoins a été réalisé soit en population, soit en milieu hospitalier selon le pays, avec un appariement avec les cas selon l'âge, le sexe et le temps. Les résultats préliminaires des études cas-témoins étaient rassurants pour le Focetria et l'Arepanrix. Pour le Pandemrix, les données issues de cette étude étaient trop peu nombreuses pour permettre de tirer de nouvelles conclusions. Le GACVS est conscient que des données supplémentaires sur le Pandemrix pourraient provenir de plusieurs pays européens, notamment dans le cadre d'un suivi prolongé d'études déjà publiées, permettant de mieux comprendre le lien entre la narcolepsie et le Pandemrix. Les données présentées à ce jour rassurent sur le fait qu'à l'exception du Pandemrix avec l'adjuvant AS03, administré à de nombreux adolescents et jeunes adultes dans plusieurs pays européens, aucune autre association notable entre l'utilisation des vaccins contre le virus grippal pandémique p2009H1N1 et la narcolepsie n'a été identifiée.

Innocuité des vaccins antityphoïdiques

Le GACVS a pris connaissance des données relatives à la sécurité de 3 générations de vaccins antityphoïdiques, notamment

⁴ See No. 3, 2016, pp. 21–32.

⁵ The Systematic Observational Method for Narcolepsy and Influenza Immunization Assessment (SOMNIA): a Study to Assess the Risk of Narcolepsy Following Adjuvanted 2009 H1N1 Influenza Vaccines. [In preparation.]

⁴ Voir N° 3, 2016, pp. 21-32.

⁵ The Systematic Observational Method for Narcolepsy and Influenza Immunization Assessment (SOMNIA): a Study to Assess the Risk of Narcolepsy Following Adjuvanted 2009 H1N1 Influenza Vaccines. [En préparation.]

Ty21a vaccine, parenteral Vi polysaccharide, and conjugated Vi polysaccharide vaccines. The Ty21a and Vi polysaccharide vaccines are currently recommended by WHO for programmatic use to control endemic and epidemic disease,⁶ while a review by SAGE for recommendations on the conjugate vaccines is scheduled for 2017.

Ty21a (currently only available as enteric-coated capsules) is recommended in individuals aged ≥ 5 years in a 3-dose (most countries) or a 4-dose regimen (in Canada and the United States); it confers protection in 62% of vaccinees for up to 7 years. The Vi polysaccharide vaccine is recommended for use as a single dose in individuals aged ≥ 2 years and confers protection in the range of $\sim 55\text{--}65\%$ for 2–3 years. Overall, Ty21a and the Vi polysaccharide vaccines are estimated to have been used in several million and several hundred thousand doses respectively over 3 decades. Both vaccines have a good safety profile, with the most common adverse events being fever (both vaccines), erythema and localized pain, and gastrointestinal events (primarily with Ty21a). Other adverse events are generally rare.

The first Vi conjugated vaccine (based on Vi antigen conjugated to a recombinant exoprotein A from *Pseudomonas aeruginosa*, (Vi-rEPA)) was evaluated in randomized control trials of $>11\ 000$ subjects in Viet Nam, and had a safety profile similar to that of the polysaccharide vaccine.^{7,8} This vaccine was not commercialized. However, 2 other conjugated Vi polysaccharide vaccines (with tetanus toxoid as the carrier protein) have been licensed by the national regulatory authority in India.

One product, the Pedatyph vaccine produced by Bio-Med Limited has been evaluated for safety in approximately 2200 subjects (immunogenicity was evaluated in 400 subjects in pre-licensure trials, while effectiveness was evaluated in 1765 subjects in a Phase IV trial). In the available published data, no safety signals have been reported and the most frequent adverse events described are local, non-specific reactions and fever.

More detailed data were presented for Typbar-TCV vaccine (produced by Bharat Biotech International Limited) which has been evaluated for immunogenicity and safety in approximately 1000 subjects pre-licensure.⁹ By the time of the meeting, more than 3 million doses of this conjugate vaccine had been distributed in the private sector. Post-licensure, the vaccine has been eval-

le vaccin vivant oral Ty21a, le vaccin polysaccharidique Vi parentéral et les vaccins polysaccharidiques Vi conjugués. Le vaccin Ty21a et le vaccin polysaccharidique Vi sont actuellement recommandés par l'OMS dans le cadre d'une utilisation programmatique pour lutter contre la forme endémique et épidémique de la maladie.⁶ Il est prévu que le SAGE examine les recommandations relatives aux vaccins conjugués en 2017.

Le Ty21a (actuellement uniquement disponible sous forme de gélules gastrorésistantes) est recommandé chez les sujets de ≥ 5 ans, selon un schéma d'administration à 3 doses (dans la plupart des pays) ou à 4 doses (au Canada et aux États-Unis d'Amérique). Il confère une protection chez 62% des personnes vaccinées, pour une période allant jusqu'à 7 ans. Le vaccin polysaccharidique Vi est recommandé en dose unique chez les individus de ≥ 2 ans et confère une protection de $\sim 55\text{--}65\%$ pendant 2–3 ans. Dans l'ensemble, on estime que plusieurs millions de doses de vaccin Ty21a et plusieurs centaines de milliers de doses de vaccin polysaccharidique Vi ont été administrées au cours des 3 dernières décennies. Les 2 vaccins présentent un bon profil d'innocuité, les manifestations indésirables les plus fréquentes étant la fièvre (pour les 2 vaccins), un érythème ou des douleurs localisées, et des manifestations gastro-intestinales (principalement avec le Ty21a). La survenue d'autres manifestations indésirables est globalement rare.

Le premier vaccin Vi conjugué (contenant l'antigène Vi lié à une exoprotéine A recombinante de *Pseudomonas aeruginosa* (Vi-rEPA)) a été évalué dans le cadre d'essais contrôlés randomisés auprès de $>11\ 000$ sujets au Viet Nam et présente un profil d'innocuité comparable au vaccin polysaccharidique.^{7,8} Ce vaccin n'a pas été commercialisé. Toutefois, 2 autres vaccins polysaccharidiques Vi conjugués (utilisant l'anatoxine tétanique comme protéine porteuse) ont été homologués par l'autorité nationale de réglementation en Inde.

L'innocuité de l'un de ces produits, le vaccin Pedatyph fabriqué par Bio-Med Limited, a été étudiée chez environ 2200 sujets (avec une évaluation de l'immunogénicité chez 400 sujets dans le cadre d'essais avant l'homologation et une évaluation de l'efficacité chez 1765 sujets dans un essai de phase IV). Les données disponibles publiées ne révèlent aucun signal de sécurité et les manifestations indésirables les plus souvent signalées sont des réactions locales non spécifiques et de la fièvre.

Des données plus détaillées ont été communiquées pour le vaccin Typbar-TCV (fabriqué par Bharat Biotech International Limited), dont l'immunogénicité et l'innocuité ont été évaluées auprès d'environ 1000 sujets avant l'homologation.⁹ À la date de cette réunion, plus de 3 millions de doses de ce vaccin conjugué avaient été distribuées dans le secteur privé. Après l'homologation, ce vaccin a été évalué dans le cadre d'une étude de

⁶ See No. 6, 2008, pp. 49–60.

⁷ Lin FYC, Ho VA, Khien HB, Trach DD, Bay PV et al. The efficacy of a Salmonella Typhi Vi conjugate vaccine in two-to-five-year-old children. *N Engl J Med* 2001;344:1263–1269.

⁸ Thiem VD, Lin FYC, Canh DG, Son NH, Anh DD et al. The Vi conjugate typhoid vaccine is safe, elicits protective levels of IgG anti-Vi, and is compatible with routine infant vaccines. *Clin. Vaccine Immunol* 2011;18:730–735.

⁹ Mohan VK, Varanasi V, Singh A, Pasetti M, Levine MM et al. Safety and Immunogenicity of a Vi Polysaccharide–Tetanus Toxoid Conjugate Vaccine (Typbar-TCV) in Healthy Infants, Children, and Adults in Typhoid Endemic Areas: A Multicenter, 2-Cohort, Open-Label, Double-Blind, Randomized Controlled Phase 3 Study. *Clin Infect Dis*. 2015;61:393–402.

⁶ Voir N° 6, 2008, pp. 49–60.

⁷ Lin FYC, Ho VA, Khien HB, Trach DD, Bay PV et al. The efficacy of a Salmonella Typhi Vi conjugate vaccine in two-to-five-year-old children. *N Engl J Med* 2001;344:1263–1269.

⁸ Thiem VD, Lin FYC, Canh DG, Son NH, Anh DD et al. The Vi conjugate typhoid vaccine is safe, elicits protective levels of IgG anti-Vi, and is compatible with routine infant vaccines. *Clin. Vaccine Immunol* 2011;18:730–735.

⁹ Mohan VK, Varanasi V, Singh A, Pasetti M, Levine MM et al. Safety and Immunogenicity of a Vi Polysaccharide–Tetanus Toxoid Conjugate Vaccine (Typbar-TCV) in Healthy Infants, Children, and Adults in Typhoid Endemic Areas: A Multicenter, 2-Cohort, Open-Label, Double-Blind, Randomized Controlled Phase 3 Study. *Clin Infect Dis*. 2015;61:393–402.

uated in a study of co-administration with measles containing vaccines (MCV), and in a Phase IV comparator study with the pre-qualified Vi polysaccharide vaccine (with a total of 470 vaccine recipients in the 2 studies). In these pre- and post-licensure studies, the adverse event profile was similar to the specific comparator vaccines in respective age groups; no safety signals were reported. However, safety follow-up was largely passive and data available limited. Data from the co-administration study (of 500 infants in 3 arms receiving Typbar-TCV alone, MCV alone, or both vaccines) showed no demonstrable interference with the immune response to either the Typbar-TCV or MCV. Post-marketing surveillance data, based on approximately 3000 reports received from pediatricians in the private sector in India, showed fever, pain and swelling were reported in approximately 1–10% of vaccinees in any age group; no serious adverse events were reported to the manufacturer. However, the overall reporting rate in this study was low and did not identify serious coincidental events that would have been expected. Based on the data presented, GACVS did not identify any new signals of serious adverse events with any of the existing typhoid vaccines. With regard to the licensed Vi-tetanus toxoid conjugate vaccines, while the safety profile appeared similar to the Vi polysaccharide vaccine, limited safety data were generated.

The Committee reviewed post-marketing safety data for one of the Vi-TT conjugate vaccines and noted limitations to the available data. It therefore recommended conducting further safety monitoring of typhoid conjugate vaccines with the following considerations: i) the need for a stronger post-marketing surveillance was highlighted, particularly in view of the lack of reported coincidental illnesses anticipated in the vaccinated age groups; ii) with large effectiveness studies of conjugate vaccine being planned, it is important that their design ensures robust safety evaluation including any potential safety risks in special population groups (e.g. malnourished children, immunocompromised individuals and, where applicable, pregnant women); iii) further safety evaluations should use the Brighton Collaboration case definitions and actively monitor serious adverse events of interest; iv) where feasible, non-specific effects of vaccination should be analysed.

Yellow fever mass vaccination campaigns using fractional dose

More than 47 countries worldwide are endemic for yellow fever (YF) and regularly experience outbreaks. Yellow fever remains endemic in South America, and East and Central Africa. Recent epidemics have occurred in southern and East Africa, particularly Angola, the southern region of the Democratic Republic of Congo (DRC) and Uganda. In 2016, over 3867 cases, with 369 deaths, were documented in Angola. Mass YF vaccination campaigns have been extensively implemented

coadministration avec les vaccins à valence rougeole (MCV), ainsi que dans une étude de référence de phase IV par comparaison au vaccin polysaccharidique Vi préqualifié (avec un nombre total de 470 personnes vaccinées dans les 2 études). Dans ces études avant et après homologation, le profil des manifestations indésirables était semblable à celui des vaccins de référence dans les tranches d'âge respectives et aucun signal de sécurité n'a été observé. Cependant, le suivi de l'innocuité a été essentiellement passif et les données disponibles sont limitées. Les données de l'étude de coadministration (chez 500 nourrissons répartis dans 3 bras d'étude, recevant respectivement le Typbar-TCV seul, le MCV seul et les 2 vaccins) n'indiquent aucune interférence manifeste avec la réponse immunitaire au Typbar-TCV ou au MCV. Les données de surveillance après la mise sur le marché, fondées sur quelque 3000 rapports communiqués par des pédiatres du secteur privé en Inde, indiquent que l'apparition de fièvre, de douleurs et de tuméfactions est signalée chez environ 1% à 10% des personnes vaccinées, indépendamment de la tranche d'âge, et aucune manifestation indésirable grave n'a été signalée au fabricant. Toutefois, le taux global de notification était faible dans cette étude et aucune des manifestations de coïncidence graves que l'on pourrait escompter n'a été notifiée. Sur la base des données communiquées, le GACVS n'a pas identifié à ce stade de nouveau signal de manifestations indésirables graves pour les vaccins antityphoïdiques existants. S'agissant des vaccins conjugués Vi-anatoxine tétanique homologués, le profil d'innocuité semble comparable à celui du vaccin polysaccharidique Vi, mais les données d'innocuité générées à ce jour sont limitées.

Le Comité a examiné les données d'innocuité recueillies après la mise sur le marché de l'un des vaccins conjugués Vi-anatoxine tétanique et a noté l'insuffisance des données disponibles. Il a donc recommandé de poursuivre la surveillance de la sécurité des vaccins antityphoïdiques conjugués en mettant l'accent sur les points suivants: 1) un renforcement de la surveillance après la mise sur le marché est essentiel, compte tenu en particulier de l'absence de notification des maladies de coïncidence pouvant être escomptées dans les tranches d'âge vaccinées; 2) les grandes études prévues pour examiner l'efficacité des vaccins conjugués doivent être conçues de sorte à permettre une évaluation rigoureuse de l'innocuité, notamment des risques potentiels dans des populations particulières (par exemple, les enfants malnutris, les personnes immunodéprimées et, le cas échéant, les femmes enceintes); 3) les évaluations supplémentaires de la sécurité devraient se fonder sur les définitions de cas établies par la Brighton Collaboration et assurer une surveillance active des manifestations indésirables graves présentant un intérêt particulier; et 4) dans la mesure du possible, les effets non spécifiques de la vaccination devraient être analysés.

Vaccination contre la fièvre jaune – campagne de masse avec des doses fractionnées

La fièvre jaune est endémique dans plus de 47 pays dans le monde, donnant régulièrement lieu à des flambées. Elle demeure endémique en Amérique du Sud, en Afrique orientale et en Afrique centrale. Des épidémies de fièvre jaune sont récemment survenues en Afrique australe et orientale, en particulier en Angola, dans le sud de la République démocratique du Congo (RDC) et en Ouganda. En 2016, plus de 3867 cas, dont 369 mortels, ont été confirmés en laboratoire en Angola. Des campagnes de masse de vaccination anti-marielle ont été menées à grande

for disease control; from 2007 to 2012, 12 campaigns have occurred in Africa with over 64 million doses distributed.¹⁰ YF vaccine is highly effective, with a single dose providing life-long protection; the safety profile of YF vaccine is well established. Although serious adverse reactions have been documented (hypersensitivity reactions, viscerotropic and neurotropic disease), these are extremely rare and often occur within defined risk groups.

Transmission of YF in 2016 was explosive, particularly in Angola (4347 suspected cases, with 377 deaths, December 2015–October 2016) and in DRC (2987 cases with 16 deaths, January–October 2016). Mass vaccination campaigns were rapidly implemented in both countries in 2016, with 30 865 375 individuals being vaccinated. Because of a global YF vaccine shortage, SAGE recommended that fractional dosage (1/5th of a dose: 0.1ml) could be used via the subcutaneous or intramuscular route. Of those vaccinated in DRC, about 50% (7.5 million) received a fractional dose. In DRC individuals aged >24 months living in Kinshasa were given a fractional dose, while infants and children aged 9–23 months living in Kinshasa or in those areas bordering Angola received a full dose.

One purpose of the GACVS meeting was to discuss the surveillance on adverse events following immunization (AEFI) in DRC following the mass vaccination campaign, with a focus on those who received fractional dosing in Kinshasa. AEFI surveillance (of serious and non-serious cases) in DRC was based on spontaneous reporting (as promoted during the campaign), on community surveys in targeted health zones reporting AEFIs, and sentinel surveillance from sentinel health-care facilities (on alert for all suspected serious cases) and through YF surveillance. The duration of surveillance for serious AEFI cases was 42 days; the vaccination campaign duration was 10 days. Given the current shortage in vaccine and the eventual need to expand the use of fractionated doses, GACVS urged DRC to conduct a detailed analysis of its AEFI reports. Wherever possible, cases with clinical presentation compatible with YF shortly after vaccination should be investigated in order to verify which virus types are involved.

GACVS strongly recommends use of the standardized tools for data collection, and harmonized tools, such as the WHO causality assessment tool, for country-level analysis of the AEFI surveillance data. This method allows for surveillance data to be aggregated, thus enhancing the sensitivity of surveillance for rare events. A comparison should be examined between those individuals who received a full dose of vaccine and those who received a fractional dose, taking into consideration any compounding factors. ■

échelle pour lutter contre la maladie. De 2007 à 2012, 12 campagnes ont eu lieu en Afrique, avec plus de 64 millions de doses administrées.¹⁰ Le vaccin antiyamari est très efficace, une dose unique conférant une protection à vie contre la maladie, et son profil d'innocuité est bien établi. Bien que des réactions postvaccinales graves aient été observées (réactions d'hypersensibilité, maladie viscérotrope et neurotrophe), ces dernières sont extrêmement rares et tendent à survenir parmi des groupes à risque bien définis.

L'année 2016 a été marquée par une transmission explosive de la fièvre jaune, en particulier en Angola (4347 cas suspects, dont 377 décès, entre décembre 2015 et octobre 2016) et en RDC (2987 cas, dont 16 décès, de janvier à octobre 2016). En 2016, Des campagnes de vaccination de masse ont été rapidement menées dans ces 2 pays en 2016, couvrant 30 865 375 personnes. En raison d'une pénurie mondiale de vaccin antiyamari, le SAGE a recommandé l'administration d'une dose fractionnée (1/5^e de la dose normale, soit 0,1 ml) par voie sous-cutanée ou intramusculaire. Environ 50% (7,5 millions) des personnes vaccinées en RDC se sont vues administrer une dose fractionnée. En RDC, les habitants de Kinshasa âgés de >24 mois ont reçu une dose fractionnée, tandis que les nourrissons et les enfants âgés de 9 à 23 mois vivant à Kinshasa ou dans les zones situées à la frontière avec l'Angola ont reçu une dose complète.

L'objectif du GACVS, lors de cette réunion, était d'étudier les données de surveillance des manifestations postvaccinales indésirables (MAPI) en RDC à l'issue de cette campagne, en s'intéressant plus particulièrement aux personnes ayant reçu une dose fractionnée à Kinshasa. La surveillance des MAPI (graves ou non) en RDC s'est appuyée sur la notification spontanée (encouragée durant la campagne), sur les enquêtes communautaires réalisées dans des zones sanitaires ciblées de notification des MAPI et dans des établissements sentinelles de soins et de surveillance, sur les alertes émises pour tous les cas graves suspects et sur le système de surveillance de la fièvre jaune. La période de surveillance des MAPI graves était de 42 jours pour une campagne de 10 jours. Compte tenu de la pénurie actuelle en vaccins et de la nécessité, à terme, d'étendre l'utilisation des doses fractionnées, le GACVS a vivement encouragé la RDC à effectuer une analyse détaillée de ses notifications de MAPI. Dans la mesure du possible, les cas dont le tableau clinique est compatible avec la fièvre jaune peu après la vaccination devraient faire l'objet d'une enquête pour identifier les types viraux impliqués.

Le GACVS recommande vivement d'utiliser des outils standardisés de collecte des données et de mener une analyse des données de surveillance des MAPI au niveau des pays à l'aide d'outils harmonisés, comme l'outil OMS d'évaluation du lien de causalité. Cette méthode permet une agrégation des données de surveillance et améliore la sensibilité de la surveillance aux manifestations rares. Il faudrait comparer les personnes vaccinées par une dose complète avec celles qui ont reçu une dose fractionnée, en tenant compte des facteurs susceptibles de biaiser cette comparaison. ■

¹⁰ Breugelmans JG et al. Reporting rates in mass campaigns. *Vaccine*, 2013, 31(14): 1819–1829.

¹⁰ Breugelmans JG et al. Reporting rates in mass campaigns. *Vaccine*, 2013, 31(14): 1819–1829.



Immunization in Practices Advisory Committee (IPAC)

Overview

Established since 2010, the Immunization Practices Advisory Committee (IPAC) is an independent committee of experts which provides external advice to WHO's Department on Immunization, Vaccines and Biologicals (IVB) on the review and formulation of policies, recommendations, standards and guidance to strengthen the delivery of vaccines at service delivery levels in line with realizing the goals of the Decade of Vaccine (2011-2020) and its Global Vaccine Action Plan (GVAP).

At the mid-point of the Action Plan, the Strategic Advisory Group of Experts (SAGE) on Immunization expressed grave concerns in 2016 on the slow progress towards increasing equitable access to lifesaving vaccines and that countries are not on track to reach 2020 targets. In response, the critical functions of the IPAC were revisited in light of need to address immunization practices at the country level through strong immunization systems, as part of broader health systems, and the continuous innovation and quality improvement of all aspects of immunization services.

These terms of reference will enter into effect in mid-2017 and IPAC membership composition will be revisited accordingly.

Mandate

The overall mandate of the IPAC is to provide independent and expert advice to the Director of WHO's Immunization, Vaccines and Biologicals Department (IVB) on how to strengthen immunization service delivery and programme management to :

- Leverage innovative approaches and technologies that can maximize reach and equitable access to vaccines up to the last mile, and to
- Optimize operational efficiency and management of vaccination programmes at country level.

The IPAC has no executive, regulatory or decision-making functions for WHO. Recommendations made and advice given by IPAC are recorded as stated and need to be approved by the Director of WHO IVB before they are formally endorsed as official WHO positions.

Critical functions

The scope of work of IPAC is organized around two principal workstreams and core areas of work.

1. – Innovations for equitable immunization coverage

The **first** critical function is to review and make recommendations on the programmatic suitability of innovative vaccine products and delivery and cold chain technologies for country level use, which are close to licensure or

licensed, but not widely adopted but have the potential to improve access to vaccines and operational efficiency of delivering vaccinations.

In particular, IPAC would provide advice and guidance on:

- Defining the programmatic needs for innovation in immunization delivery;
- Identifying and prioritizing innovative products, technologies, and practices which are close to licensure or licensed, to strengthen national immunization programmes; and
- Assessing the programmatic suitability of such products, technologies, and practices for broader country roll-out.

2. – Immunization Service Delivery and Programme Management

The **second** critical function is to provide advice, recommendations and guidance on immunization practices to strengthen routine immunization programmes. This workstream of the IPAC would focus on best practices and new approaches to strengthening immunization programme implementation at country level within the broader health systems context including novel approaches and strategies to:

- Design service delivery strategies to reach the unreached ;
- Integrate immunization services with other health interventions;
- Optimize immunization supply chain systems; and
- Improve operational efficiencies and management of national immunization programmes (including human resources and immunization data management).

Linkages with other WHO Advisory Bodies, Expert Committees/Groups

The work of IPAC will be conducted in synergy with the existing network of WHO advisory committees as follows:¹

Relation to the Strategic Advisory Group of Experts (SAGE) on immunization: IPAC regularly takes note of outcomes of SAGE meetings and decisions, assists in operationalizing SAGE recommendations for country practice and reports to SAGE on IPAC deliberations and activities. IPAC recommendations which could potentially lead to policy changes are regularly brought to the attention of SAGE. SAGE may involve IPAC in discussions on operational and implementation issues and request IPAC to provide evidence-based reviews of such issues, drawing upon IPAC's unique country and field experience.

Relation to the Product Development for Vaccines Advisory Committee (PDVAC): PDVAC appraises upstream vaccines and technologies including novel delivery platforms, reviews clinical and regulatory pathways, and defines Preferred Product Characteristics (PPCs). IPAC may provide operational and programmatic suitability expertise to PDVAC for the development of value propositions of new vaccines and technologies. IPAC and PDVAC may set up joint working groups. IPAC programmatic expertise related to more upstream, i.e. not yet licensed, products, tools and technologies is channelled through PDVAC, e.g. for the development of PPCs.

Relation to the Immunization and Vaccines Related Implementation Research Advisory Committee (IVIR-AC): IVIR-AC reviews research methods and quality of information for impact evaluation assessments, reviews operational research methods to minimize barriers and improve coverage, and defines improved methods for monitoring of immunization programmes. IPAC may provide country-level expertise to IVIR-AC as needed and request IVIR-AC to assist with defining and conducting the necessary research. IPAC and IVIR-AC continuously coordinate work on overlapping themes related to operational research and monitoring of immunization programmes.

¹ The hierarchy of WHO immunization-related advisory committees and their interactions and demarcations is further described here: http://www.who.int/immunization/policy/WHO_vaccine_development_policy.pdf?ua=1

Relation to the Programmatic Suitability of Vaccine Candidates for WHO Prequalification Standing Committee (PSPQ-SC): PSPQ-SC is an independent body reporting to the Director WHO EMP. Two IPAC members are part of the PSPQ-SC. IPAC must be involved in any further development or change of criteria of PSPQ process. IPAC has, however, no distinct role of endorsing PSPQ-SC recommendations.

Relation to other WHO advisory boards: IPAC proactively communicates and shares information with other WHO immunization and non-immunization advisory boards and expert committees, such as the Expert Committee on Biological Standardization (ECBS) and the Global Advisory Committee on Vaccine Safety (GAVCS). In some cases, where IPAC recommendations have specific safety or standards implications, these are formally brought to the attention of the relevant committee for review.

Membership and Observers

The IPAC comprises 11 members, who serve in their personal capacity. To be considered as an IPAC member, individuals must be recognized experts in the field of immunization and can be either nominated or self-apply.

The membership of IPAC seeks to reflect a representation of the following:

- Areas of expertise: Immunization service delivery, programme design, operations and management of immunization programmes, immunization products, tools and technologies, vaccine and logistics management, information systems, monitoring and evaluation, regulatory issues and health systems strengthening.
- Professional affiliation: Immunization programme managers, public health specialists, medical professionals, academics, representatives of civil society and of governmental or non-governmental organizations.
- Geographic and gender balance: All efforts are made to ensure equitable geographic and gender balance.

IPAC members are appointed by the Director WHO IVB in light of recommendations made by a selection panel, following a broad public call for nominations. The selection panel is designated by the Director WHO IVB and consists of two senior IVB staff (including one staff from the IPAC Secretariat), the IPAC chair and three observers and follows an established protocol.

Prior to being appointed to the IPAC or to the renewal of a term, nominees and members are required to complete a WHO declaration of interest form and a confidentiality undertaking.

IPAC members are appointed to serve for an initial term of three years, which can be renewed once. Appointments are renewed by the Director WHO IVB, in consultation with the IPAC chair and Secretariat.

Observers representing the following organizations are regularly invited to all IPAC meetings: WHO Regional Offices, UNICEF Programme Division and Supply Division and the Gavi Secretariat. Other observers representing global immunization partners such as the Bill and Melinda Gates Foundation, the US Centers for Disease Control and Prevention, the European Centre for Disease Prevention and Control, PATH, John Snow Inc., Agence de Médecine Préventive, Médecins Sans Frontières, the International Federation of Pharmaceutical Manufacturers & Associations, the Developing Countries Vaccine Manufacturers Network and others, are invited to attend IPAC meetings in view of the agenda items discussed. Observers represent their institutions and do not serve in their personal capacity. It is expected that observer institutions are represented by one and the same person for a continuous period of time. Observers are invited to all open IPAC sessions, but have no voting rights.

All background documents, papers, presentations and reports presented to IPAC shall be treated as confidential and may not be publicly disclosed or used by members or observers without prior approval by WHO. Detailed reports are released and published regularly after each IPAC meeting.

As a WHO advisory committee, neither IPAC as a whole, nor individual members can speak or act on behalf of WHO, or attend meetings on behalf of WHO without prior consent from WHO. Correspondence with outside parties on IPAC issues must be copied to the WHO Secretariat in all cases. IPAC members may be approached outside of meetings for their views, comments and statements on particular matters of public health concern and asked to state their views, as a member of IPAC, or speak to the views of the committee. Members shall refrain from commenting and refer such enquiries to the WHO Secretariat.

Membership in IPAC may be terminated at the discretion of the Director WHO IVB for any one of the following reasons: a) Failure to attend two consecutive IPAC meetings; b) Change in affiliation or status, resulting in a conflict of interest; or c) Lack of professionalism, such as a breach of confidentiality, or misrepresentation of IPAC or of WHO IVB.

Role of Chair

The chair of IPAC is appointed for a non-renewable three-year term by the Director WHO IVB. Eligibility for the post of chair is dependent on having previously served on IPAC for a period of not less than one year. The person appointed as chair should have a broad knowledge of the full scope of the areas of work that concern IPAC, and have proven meeting management and chairing skills.

The chair, together with the WHO Secretariat, sets the IPAC meeting agenda, plans the modalities of discussion of each agenda item and coordinates recommendation sessions. The chair provides regular updates to SAGE on all issues dealt with by IPAC. The chair may also be required to attend other WHO meetings as appropriate.

Role of Members

IPAC members have the responsibility to provide the Director WHO IVB with high quality, evidence-based and independent advice and recommendations on the agenda topics discussed by the committee. In all cases, the work of IPAC and its working groups will strive to improve WHO IVB's ability to support countries in improving their immunization programmes and to increase equitable immunization coverage in line with the strategic objectives of the Global Vaccine Action Plan. This requires that IPAC as a whole and IPAC members individually work hand-in-hand and in full trust with the WHO Secretariat and relevant WHO counterparts.

IPAC members are expected to:

- participate in annual face-to-face meetings, review all background documents and materials and circulate presentations and other inputs prior to these meetings;
- participate in regular web-based meetings and actively contribute to IPAC online discussions in relevant fora and to IPAC publications;
- actively engage in IPAC working groups and task teams along with specific topic experts and WHO staff;
- represent IPAC in other WHO departmental, cross-departmental or other meetings at the request of meeting organizers, as advised by the IPAC chair and Secretariat.

Meetings and Operational Procedures

IPAC is expected to meet once per year face-to-face. The working language of IPAC is English. All members are required to attend and contribute to these meetings and to the development of meeting agendas. A two-year rolling calendar with dates for the next meetings and potential agenda items is made available for members and observers to plan in advance. IPAC utilizes an online discussion forum, open to IPAC members and observers, for further deliberations of IPAC matters.

In addition to the annual meetings, active participation is expected from all IPAC members throughout the year, including participation in regular web-based meetings, in IPAC working groups and task teams, in IPAC online discussions and in interactions by email.

IPAC decisions are taken by consensus and care is taken that decisions are based on the best quality and most up-to-date evidence. No IPAC decisions are taken in the online forum. For decisions to be taken outside the regular meetings, separate calls are organized by the Secretariat.

IPAC meetings are, in principle, open to all interested parties. In addition to members and observers, WHO may invite additional specific topic experts, including, but not limited to, representatives of technical agencies, non-governmental organizations, civil society, professional organizations, donor organizations, as well as developers and manufacturers of vaccines and immunization technologies. Chairs of IVIR-AC and PDVAC are regularly invited to attend IPAC meetings. Background documents and other materials are distributed via the IPAC website and online forum a minimum of two weeks prior to the meetings.

Before IPAC recommendations are accepted as a WHO position, they must be reviewed and formally endorsed by the Director WHO IVB. A summary of the IPAC meeting reports covering the main issues discussed and the resulting IPAC statements or recommendations will be published in the Weekly Epidemiological Records within 2 months of each meeting.

A repository of IPAC meeting reports and IPAC statements is regularly updated on the IPAC website at http://www.who.int/immunization/programmes_systems/policies_strategies/ipac/en/

Conflict of Interest and Confidentiality

IPAC members are required to regularly disclose potential conflicts of interest, which are reviewed by the IPAC Chair and the Secretariat. In case of a determined conflict of interest of an IPAC member, the following options may be applied by the WHO Secretariat in consultation with the IPAC chair: The member may be invited to continue to participate in the meeting or work, provided that the interest is publicly disclosed; The member may be asked not to take part in the portion of the meeting, discussion or work related to the interest or not participate in related decisions; or the member may be asked not to take part in the meeting or work altogether.

IPAC makes every effort to maintain confidentiality and holds closed sessions, if and when required.

Working Groups and Task Teams

IPAC working groups are established on specific priority themes by the IPAC Secretariat in consultation with the IPAC chair and act as additional resources, providing a specific set of expertise, not available in the full committee.

Working groups have distinct terms of reference including goals and objectives, processes, timelines and deliverables.

Working groups deliver their pre-defined output to the full committee during the annual face-to-face meetings and may provide additional information or request committee feedback on their proceedings during the regular online meetings. Once work towards the terms of reference of the working group is completed and successfully presented to the full committee, the group is terminated.

IPAC task teams are convened on an as-needed basis by the IPAC Secretariat in consultation with the IPAC chair. Task teams are established on a time-limited basis to deliver a defined output on a specific topic of interest. Task teams normally accomplish their tasks through the collection, description, analysis and presentation of available evidence. Once their output is successfully delivered to the full committee, the task team is dissolved.

Generally, a working group or task team will include one, maximum two IPAC members and a WHO focal point who will take the lead in the preparations and discussions of the group or task team.

Further details on purpose, structure and functioning of the working groups and task teams can be found in Appendix A.

Appendix A:

Purpose, Structure and Operational Procedures for IPAC Working Groups and ad-hoc Task Teams

Purpose of establishing a working group

Working groups are established by the WHO IPAC Secretariat in consultation with the IPAC chair. Working groups help to address specific questions identified by IPAC that require a specific set of expertise not available in the full committee. Working groups are intended to increase the effectiveness of IPAC deliberations by providing evidence-based information and options for recommendations - as well as the implications of each of the various options – to the full committee.

Working group TOR

Each working group operates under specific terms of reference, developed jointly by the working group chair and the WHO IPAC Secretariat and approved by the IPAC chair and the Director WHO IVB. Working group TOR define distinct goals and objectives, processes, timelines and deliverables.

Working group composition

A working group will normally consist of 5 to 9 members and include one or two IPAC members - one of whom will act as working group chair - and a WHO focal point, who will assist with the operations of the working group. Additional subject matter experts, selected to meet the required expertise and serving in their personal capacity, may be included in the working group. Occasionally the working group chair, in consultation with the WHO Secretariat, may request participation of additional experts, who are not members of the working group, on an ad-hoc basis.

Working group functions and reporting

Working groups provide a service to IPAC by gathering and organizing information and evidence upon which IPAC can deliberate. Working groups do not render advice or recommendations directly to the Director WHO IVB and working group chairs and members or participating experts are not empowered to speak on behalf of IPAC. The actual process of deliberation resulting in development of group consensus and IPAC recommendations occurs only in the public open forum of IPAC meetings.

Brief summary minutes of each working group meeting, approved by the working group chair, are submitted to the WHO IPAC Secretariat within 2 weeks of each working group meeting and are immediately posted on the IPAC website. In addition, working groups deliver a presentation and submit a brief narrative report to the full committee during the annual IPAC face-to-face meetings, covering working group deliberations, outputs and deliverables. Working groups may provide additional information and/or request committee feedback on their proceedings during the regular IPAC online meetings.

Once per year, based on all presentations and reports, the full committee will review the set-up of each working group, its processes and deliverables and will issue a recommendation on its termination or continuation to the IPAC Secretariat.

Working group operational procedures

The working group chair, in consultation with the WHO focal point, will establish an annual work plan for the group. Working groups are expected to accomplish most of their dealings through web-based or teleconferences, which should be scheduled well in advance with set dates and times. In addition, working groups will exchange emails and/or use the IPAC online discussion fora. Face-to-face meetings of working groups may facilitate progress. Such meetings should normally be scheduled in association with the annual IPAC meetings and be anticipated at least 2 months in advance.

WHO supports travel costs for the duration of IPAC meetings for IPAC members, WHO Regional Advisers and experts invited to present at the meetings. WHO may support travel for additional persons for the purpose of a working group meeting, as appropriate. Such requests should be submitted to the IPAC Secretariat for consideration on a case-by-case basis, with justification for any additional costs incurred.

Working Group Conflict of Interest

Working groups fully abide by the IPAC conflict of interest procedures. Prior to being appointed to a IPAC working group or to the renewal of a term, nominees, members and invited experts are required to complete a WHO declaration of interest form and a confidentiality undertaking.

In case of a determined conflict of interest of a working group member or invited expert, the following options may be applied by the WHO IPAC Secretariat in consultation with the working group chair: The member or invited expert may be invited to continue to participate in the meeting or work, provided that the interest is publicly disclosed; The member or invited expert may be asked not to take part in the portion of the meeting, discussion or work related to the interest or not participate in related decisions; or the member or invited expert may be asked not to take part in the meeting or work altogether.

Task Teams

IPAC task teams are convened on an as-needed basis by the IPAC Secretariat in consultation with the IPAC chair. Task teams are set-up with the aim of collecting, analysing and summarizing available evidence on specific IPAC topics of interest, particularly when such a task is determined to be extensive or particularly complex (e.g. systematic reviews). Task teams deliver their requested output to the full committee as basis for IPAC's deliberations on the specific topic and/or the development of recommendations.

Task teams may include external institutions and agencies delivering contract research. Task teams will include one to two IPAC members and a WHO focal point who will oversee and guide the set-up, preparations, dealings and outputs of the task team. Task teams are strictly time-limited and will be dissolved by the IPAC Secretariat, once the agreed deliverables have been submitted to the full committee.

Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC): summary of conclusions and recommendations, 1-2 February 2017

THEME: Research to minimize barriers and improve coverage of vaccines currently in use

Session 1: Non-specific effects (NSE) of vaccines

Introduction

Between February 2016 and January 2017, the WHO Secretariat convened three consultations of the same group of experts to review NSE hypotheses that researchers have advanced, possible research questions that are related to these hypotheses, and trial designs that could effectively address such questions. In June 2016, IVIR-AC reviewed the ongoing work and acknowledged the progress made towards the refinement of priority research questions and the outlined trial designs. At the February 2017, the Committee was presented with two proposed trial designs developed through the ad-hoc expert consultations.

Recommendations

- IVIR-AC endorsed the value of definitive evidence to confirm or refute the existence and magnitude of the impact of non-specific effects of vaccines on susceptibility to severe childhood infection in low and middle income countries, especially attributable mortality, and the potential follow-on implications for national immunisation schedules.
- IVIR-AC agreed that the two proposed trials emerging from the three ad-hoc expert consultations in 2015 and 2016 were the best options among the possible research questions and trial designs considered. Further development of these proposals will require careful consideration of the balance between feasibility and required sample size to exclude an impact on childhood mortality of public health importance, taking into consideration that the very implementation of a clinical trial is likely to reduce mortality in all arms.
- IVIR-AC noted that the required size and location of the trials will make them technically challenging and expensive to implement. If the trials are implemented, it is important to select sites carefully, with respect to both site and investigative team capacity and generalizability of trial findings. This will require a high level of coordination with national authorities and local stakeholders.
- IVIR-AC will review and comment on the two proposed protocols while they are being finalised.

Session 2: Tools to operationalize the WHO recommendations on the licensed dengue vaccine

Introduction

IVIR-AC agreed that the dengue seroprevalence survey guidelines, modelling using age-specific incidence data and transmission intensity map are useful tools. However, IVIR-AC affirmed the importance of maximising the efficiency of implementation of seroprevalence surveys, and further assessment should be given to opportunities to do so. These two activities should be well coordinated to inform the others.

Recommendations

The survey guidelines should be modified or expanded to take into account issues relevant to feasibility and value for effort expended such as:

- Ensuring serologic criteria used by serosurveys are as comparable as possible to those used in the clinical trials of vaccine.
- Greater clarity with respect to criteria for high, medium and low prevalence strata.
- Better definition of the required level of assay sensitivity and specificity to enable an informative assessment of seroprevalence in each stratum.
- More detailed consideration of the influence of covariates other than age and school attendance.
- Given the lack of capacity for neutralisation assays in many settings, identifying laboratory capacity to process neutralisation assays (validation purposes) for serum collections obtained in other countries would be valuable.
- The ethical implications of an opt-out approach for participation as well as the feasibility and utility of disclosing and explaining results to individual participants should be considered in accordance with usual practices for serosurveys and the situation in country.

To improve efficiencies, the following should be considered:

- The validity of salivary samples as an alternative to serum has been shown for some viral infections such as measles and rubella. Consideration of salivary samples, both as a means to increase study participation, and/or their collection simultaneously with serum to allow further studies of validity is potentially worthwhile in the context of this substantial global effort.
- Similar opportunities to enhance efficiency may arise from simultaneous opportunistic collection of residual blood samples from diagnostic laboratories, or existing biobanks from previous seroprevalence studies on other pathogens, in the same age groups. Comparable findings from opportunistic residual and purposive sampling have been found for measles in a high-income country setting and this may be an appropriate option in regions with adequate public access to laboratory testing.
- Efficiency will also be improved if the blood samples taken can also be used to address questions for other pathogens (e.g. as part of the assessment of measles elimination) or stored for future use, but this also has ethical implications for consent procedures.

While the value of the global dengue transmission map is appreciated, there is potential for misinterpretation of the map predictions that may be counter-productive to informed decision-making. To minimise the risk, the following steps should be taken:

- The map should be pilot tested to ensure the comprehension and interpretation is sufficiently clear, including consideration of appropriate disclaimers before it is made publicly available.
- The methods tab text needs more detail. This tab could also be adapted to show a more specific explanation of the data limitations for each of the selected outputs.
- Hover text should be incorporated over the map that reveals the source of information for each estimate (eg. local surveys, extrapolation from other settings).
- The benefits and limitations of the map for different potential uses should be made clear, e.g. identifying data gaps, informing national decisions, informing vaccination decisions by individuals.
- The use of traffic light colour schemes on the map should be avoided as they may be misconstrued.

- The limited granularity in the map may create challenges in interpretation because of spatial heterogeneity in seropositivity within each geographical unit. This should be clearly caveated, and the impact of such heterogeneity on impact predictions should be explored in modelling.
- When new data are obtained, how close the previous predictions were to these data should be shown, along with how the results are changed by the new data.
- Showing potential vaccine impact can be useful, but this should be done only when such estimates are deemed to be sufficiently robust.
- There is a need to deliberately collect/collate data on African countries.

In addition, IVIR-AC would appreciate a more detailed description of the machine learning approach for producing the map. The Committee also recommends working with other groups doing similar work, as well as cross-validation with serosurveys as they become available.

THEME: Research to conduct impact evaluation of vaccines in use

Session 3: Measles mortality model

Introduction

The methods used were reviewed by QUIVER (former IVIR-AC) in 2011. Since then several major methodological innovations have been incorporated, including (i) adding explicit age structure to estimates of cases (so that model outcomes can be fitted to age-specific case data that are now collected by WHO), (ii) changing the function relating the proportion of susceptibles in the population to the annualised attack rate to better approximate the threshold nature for herd effects, and (iii) Stochasticity in the new model is now represented as binomial, rather than Gaussian as in the original model.

Recommendations

- IVIR-AC agreed that the updated data providing information on the age stratification of measles cases is an improvement, but cautioned that input data remain subject to reporting biases such as underreporting in outbreak situations, underreporting of subclinical, atypical cases and misdiagnosis, and that there are important within-country heterogeneities.
- Work to validate the functional form used by the current model to relate susceptibility to the annualised attack rate by comparing it to a fully dynamic SIR model is valuable and if not done, a justification for this should be articulated. The impact of incorporating age specificities in the functional form should be explored.
- There is a need to take into account additional coverage variables, including the association between MCV1, MCV2 and SIA coverage, as well as the duration of high MCV coverage.
- CFRs are likely to change over time, and should be explicitly taken into account when updated information becomes available.
- It is important to understand and communicate the reasons for the differences between estimates of global measles burden by WHO and other groups. A systematic comparison of measles disease burden models would be helpful.
- Data limitations that affect the ability to fit models to age-specific case data from India, especially those related to between region heterogeneity, should be explored.

Session 4: Hepatitis B vaccine impact model comparison study

Introduction

The WHO Global Hepatitis Programme (GHP) and the Immunization, Vaccines and Biologicals (IVB) departments decided to collaborate to request IVIR-AC to compare the methodological approaches that have been used to estimate the Hepatitis B surface Antigen (HBsAg) prevalence in children 5 years of age, and sought the comments from IVIR-AC. The impact model comparison study should be done on the basis of epidemiological and service coverage estimates in terms of model structure and design, assumptions, data inputs. The objective is to identify and understand the most influential drivers of variation of the model estimates.

Recommendations

- IVIR-AC agreed with the overall plan and approach to reviewing and synthesising results from hepatitis B models with calibrated data sets and to leave aside disease progression for another comparative modelling exercise.
- The review should be expanded to include models set in high-income countries that could still be applied to LMIC settings, and static models, partly to ensure that the number of models is sufficient to draw conclusions. To this effect, the date range could also be gradually expanded to encompass a longer period than currently proposed (2009 – 2017). The feasibility of engaging researchers with models published over 10 years ago seems questionable, but may need to be investigated if the number of included models would otherwise be insufficient.
- Changes in hepatitis B prevalence beyond 5 years old should be included as a secondary outcome.
- The research question for which each model was developed should be included in the data extraction form.
- For pooled models, further methodological thinking is needed concerning objective criteria for assessing and weighing the models and on using jack knife methods to examine robustness for excluding models.
- Through systematic literature reviews and a call for interest relevant modelling groups should be identified and be brought together.
- Stratified analysis based on country epidemiology (very low, low, intermediate and high endemicity) categories may be useful.

Session 5: Typhoid vaccine impact and economic models

Introduction

Currently WHO Strategic Advisory Group of Experts (SAGE) on immunization recommends vaccinating high-risk groups and populations against typhoid in the context of other control strategies. However, there is limited vaccine uptake at the moment. Conjugate vaccines with longer duration of protection compared to previous vaccines, and which appear to be immunogenic in infants, have recently become available though not widely licensed. Modellers at the Yale School of Public Health and the University of Antwerp have developed a vaccine impact model and cost-effectiveness analysis. This work has value in informing updated to the typhoid vaccine policy recommendations by SAGE in October 2017.

Recommendations

IVIR-AC appreciated the clear and transparent description of the typhoid modelling work, such as presentation of the model structure and fit to data. The epidemiological modelling work is sophisticated and well done, but both transmission modelling and economic evaluation aspects were noted to have data limitations at the moment. In particular, there were concerns over use of older data (eg. WHO-CHOICE costs from 2004), extrapolation of Zanzibar cost data to the Kenya setting, failure to acknowledge differential costs between urban and rural settings, and use of private sector user charges as a direct proxy of opportunity costs.

Key areas that should be improved include the following:

- Findings from the model should be considered in the context of other available typhoid vaccines (besides the conjugate vaccine) and non-vaccine interventions to control typhoid such as access to improved water, sanitation and hygiene (WASH) facilities. IVIR-AC noted the apparent lack of appropriate data for the latter analyses in the model. Further analysis may be more descriptive than quantitative recognising the potential challenge to interpret the direct impact of each intervention on disease reduction in a quantitative model.
- The impact of antibiotic use and antibiotic-resistant strains of typhoid should be considered, and if it is not included, its likely impact should be discussed.
- More realistic vaccine prices (besides \$1/dose) should be used, including in the base case.
- The use of 1-3xGDP/capita fixed cost-effectiveness thresholds should be avoided as they are not recommended by WHO for priority setting for country level decision-making.
- Data on hospitalisation rates, hospitalisation costs and age-specific case fatality rates (CFRs) should be improved, particularly for the 54 country modelling.
- The role of chronic carriers and asymptomatic/mild infection on disease transmission should be further investigated. If indirect (herd) protection is found not to have an important effect on cost-effectiveness, then this would justify future use of a static model for cost-effectiveness analyses on typhoid fever vaccination. This is partly because a static model is more transparent and adaptable to end-users.
- Uncertainty ranges around parameters should genuinely reflect model and parameter uncertainty since they are crucial to the value of information analysis.
- The use of malaria cost data to estimate the cost of managing typhoid could be an underestimation of the cost implications.

The vaccine impact and cost-effectiveness models should continue to be improved as data on varying level of disease burden in different settings, transmission, vaccine effectiveness and health care costs become available.

Session 6: Reporting guide for observational influenza vaccine effectiveness studies

Introduction

Observational studies can be used to inform uptake of influenza vaccines in National Immunization Programmes. However, such studies are susceptible to bias. Examples of such bias include the finding of a recent meta-analysis that the effectiveness of influenza vaccine against all-cause mortality is greater than its effectiveness against influenza-specific endpoints of hospitalisation for pneumonia and influenza-like illness (ILI). The proposed reporting guide for observational influenza vaccine effectiveness (VE) studies will be helpful to researchers and reviewers.

Recommendations

- IVIR-AC recognizes the value and supports the aim to develop a reporting guide for observational studies of influenza VE. IVIR-AC focal points have been identified to assist with further development.

- IVIR-AC recommends that development of this reporting guide not be construed as requirements for publication, although stratification of priorities (i.e., essential, desired and encouraged) may be appropriate.
- The guide should consider how to address potential sources of bias, such as health-seeking behaviour and confounding for both risk of ILI and likelihood to be vaccinated. The guide may indicate approaches to adjustment for such bias. Estimates of VE should also be accompanied with analysis of antigenic matching of the circulating strains, vaccine formulations, availability and access insofar as possible, and acknowledged in limitations if relevant data are unavailable.
- As a first step, the guide should focus on reporting VE studies, it may then also consider implications for enhancing test-negative study designs based on investigators' study aims and available data.
- IVIR-AC recognizes potential to extend comparable and appropriately adapted recommendations for VE studies for vaccines against other diseases. Collaboration with other groups developing guidelines (e.g. STREngthening the Reporting of OBServational studies in Epidemiology (STROBE)) may be helpful in that regard.

09-10 February | 2017

13th Meeting of the SAGE Polio Working Group

Conclusions and recommendations

Note for the Record



DRAFT AS OF 4/4/173/20/17

Background

The 13th face-to-face meeting of the SAGE Polio Working Group (WG) was held during 9-10 February 2017 at the World Health Organization in Geneva, Switzerland.

The meeting was attended by the following WG members: Dr. Zulfiqar Bhutta, Dr. Walt Dowdle, Dr. Peter Figueroa, Dr. Nick Grassly, Dr. Ilesh Jani, Dr. Youngmee Jee, Dr. Jacob John, Dr. Liz Miller, Dr. Jeffrey Mphahlele, Dr. Walt Orenstein, Dr. Kimberly Thompson, and Dr. K Zaman.

Dr. Yagob Al-Mazrou (Chair) was unable to attend so Dr. Figueroa acted for the Chair.

This note presents a summary of the main findings, conclusions, and recommendations of the meeting.

Context and objectives of the meeting

In October 2016, SAGE reiterated its concern over the global supply shortage of Inactivated Poliovirus Vaccine (IPV), which will persist into 2017-18. Given this situation and the high efficacy of 2-dose fractional intradermal IPV, SAGE strongly recommended that: countries should start preparing for a fractional intradermal 2-dose IPV schedule, e.g. at 6 and 14 weeks, in lieu of a single intramuscular full dose at 14 weeks.

SAGE also reviewed the Polio WG discussion on future polio immunization policy and requested the WG present its recommendations on future immunization policies for consideration by SAGE in April 2017.

The specific objectives of the WG meeting were:

1. To review the GPEI programme update, including the IPV supply situation
2. To review scientific data on the use of IPV in polio eradication, outbreak response and routine immunization
3. To make a proposal on future immunization policy (including duration of vaccination with IPV after OPV withdrawal (i.e., post-OPV immunization schedule) for the April 2017 SAGE meeting.

Topic 1: GPEI programme update

The WG reviewed the GPEI programme update, presented by Michel Zaffran (WHO), IPV and OPV supply situations, presented by Ian Levis and Ann Ottosen (UNICEF) and Diana Chang-Blanc (WHO), and epidemiology of Vaccine-Associated Paralytic Poliomyelitis (VAPP) after the tOPV to bOPV switch in India by Ondrej Mach (WHO).

Progress toward interruption of WPV1

The GPEI reported significant progress in the elimination of WPV1 in Afghanistan and Pakistan in 2016, with 20 WPV1 cases in Pakistan and 13 in Afghanistan with onset of paralysis in 2016 (as of February 26, 2017), which represent significantly lower numbers than in 2015 (i.e. 54 cases in Pakistan and 20 cases in Afghanistan). The GPEI reported on three transmission corridors: Nangahar/Kunar-Khyber Peshawar (last case reported February 2016), Pakita-FATA/KP (where WPV1 circulation continues in Bermal, Afghanistan, but not reported on the Pakistan side over the last 6 months), and Kandahar/Helmand-Baluchistan (WPV1 and VDPV2 circulation continues). The GPEI reported aggressive response in this area and no cases in Karachi since January 2016. In both countries, AFP surveillance indicators meet minimum required standards of quality.

In Nigeria, the GPEI reported four WPV1 cases in July and August 2016 in Borno, but no WPV1 cases or isolates in environmental surveillance since then. However, most of Borno state continues to be inaccessible, significantly affecting the quality of surveillance and Supplementary Immunization Activities (SIAs). While Borno has overall good AFP indicators, there are few AFP cases reported from inaccessible parts of Borno.

cVDPV2

Since the tOPV-bOPV switch in April 2016, the detection of Sabin viruses in most OPV-using areas appears to have declined as expected. The GPEI reported 20 VDPV2 isolations from environmental or AFP surveillance with 3 cVDPV2 outbreaks confirmed (i.e. Borno and Sokoto in Nigeria, Quetta in Pakistan) and two pending

classification (Chechen Republic/Moscow (Russia) and Mozambique). The cVDPV2 case in Borno is a persistent cVDPV2 from the pre-OPV2 withdrawal period (37 nucleotide changes from Sabin). The Sokoto, Nigeria (12-17 nucleotide changes) and Quetta, Pakistan (9-18 nucleotide changes) outbreaks most likely represent viruses derived from OPV used before the switch, and they demonstrate that some areas failed to conduct sufficient good quality tOPV rounds prior to the switch to prevent the development of cVDPVs post-switch. The GPEI responded to the Nigeria/Pakistan outbreaks with mOPV2. Detection of Sabin virus in AFP cases and environmental surveillance in some countries (e.g. India, Iraq and Nigeria) after the switch revealed some limited continued use of tOPV, which triggered thorough investigations.

Containment

The GPEI established the Containment Working Group (WG) to support the Global Certification Commission (GCC) in its oversight role of GAPIII, and the Containment Advisory Group (CAG), which reports to the Director General of WHO, to provide scientific guidance on containment related matters. As of 16 January 2017, 30 countries reported the designation of 78 Poliovirus Essential Facilities (PEF), which plan to retain infectious and potential infectious poliovirus materials after OPV cessation.

Transition planning

The GPEI continues the process of developing a strategy for after certification of all WPV eradication. The post-certification strategy aims at defining the essential functions that need to be sustained to maintain a polio free world post certification. The high level goals of the strategy include: 1) contain polio sources, 2) detect and respond to any outbreaks, 3) protect populations (including post-certification strategy such as bOPV cessation) and 4) manage effectively and monitor to ensure ongoing polio functions are embedded in existing structures (e.g. beyond GPEI as required) and are properly monitored to sustain a polio free world.

IPV and OPV supply situations

The WG reviewed the current IPV and OPV supply situations. IPV supply continues to fall short of demand, with one manufacturer reducing projections even further since the last WG call in December 2016. Manufacturers are supplying only 50% of the UNICEF-originally awarded quantity for 2014-2018 (e.g. expected supply of ~50M in 2017 vs. contracted amount of ~110M). One supplier was able to improve phasing of their committed supply through a general improvement of the monthly production plan and was able to reallocate 1.5 million doses from another customer. A potential additional quantity of up to 1.6 million doses will be confirmed end of March 2017, and possible additional quantities may become available in Q4, to be confirmed later in the year. The other supplier reported a further decline in supply (~4M doses), with no strategies available to address this shortfall from this supplier. To close the gap between expected supply as of December 2016 and current expectations, the options include i) interrupting supply to Tier 2 countries until October 2017; ii) request Tier 2 countries to adopt a fractional IPV schedule (which would not be a short term solution); or iii) postponing the availability of 2 million doses initially kept in reserve for outbreak response/SIAs from June to November 2017. The prospects for supplying IPV to Tier 3 and 4 countries now appear delayed until sometime in 2018. The current UNICEF tender contract expires at the end of 2018, so UNICEF will issue a new tender in Q2 2017.

A preliminary cost analysis by Kid Risk indicated that a two fractional doses schedule instead of 1 full IM dose may help alleviate the IPV supply situation and reduce costs (with BCG needles and syringes), if logistically feasible, but it may also have a substantial impact on industry's incentives to invest in production.

The WG also reviewed the bOPV and mOPV supply situations. UNICEF will maintain 150 million doses as a bOPV buffer in finished product, reaching 150 million doses in June and maintained throughout 2017. UNICEF noted the mismatch between the WG recommendations from the prior meeting to maintain high levels of bOPV demand to support regular continued SIAs between now and bOPV cessation and the current GPEI SIA placeholder calendar, which has a high intensity of pre-cessation campaigns. The WG raised concerns about the future availability of OPV in the context of delays in achieving eradication and implementing bOPV cessation. Overall, the programme originally procured 1.12 billion doses of mOPV stockpile (519 million doses of type 2, 300 million doses of type 1 and 300 million doses of type 3, down from the originally planned 2.5 billion due to reduced budget). Currently, there are 24 million doses of finished mOPV2 available in the

stockpile through to end of March with pending awards of 119 million doses for October/December 2017 delivery, totalling 269 million doses. This reduces the mOPV2 bulks in the global stockpile to 250 million doses. To revisit the size, composition, timelines and structure of the stockpile and provide guidance for the future based on initial experience, the GPEI established a cross-functional Polio Stockpile Working Group to report back in Q2 2017.

VAPP epidemiology after the switch

Lastly, the WG reviewed the epidemiology of Vaccine-Associated Paralytic Poliomyelitis (VAPP) after the tOPV to bOPV switch in India. The VAPP risk in India appears significantly decreased since the introduction of IPV and the switch, with no VAPP related to type 2 reported and a reduced number of VAPP cases associated with OPV1 and OPV3 and an increased age of VAPP cases among zero-dose and one-OPV-dose children.

WG decisions/recommendations

- The WG noted the progress in the elimination of WPV in Afghanistan and Pakistan and the improvement of surveillance in Pakistan. However, the WG concluded that the GPEI must address significant remaining gaps in all 3 endemic countries to achieve elimination of WPV and cVDPV2. These gaps include the unreliability of SIA monitoring data (e.g. LQAS and independent monitoring indicating high level of immunization coverage despite ongoing transmission), inadequate surveillance, and inaccessibility as a result of insecurity (as demonstrated in isolation of cVDPV2 in Borno with 37 nucleotide changes from Sabin) and not immunizing repeatedly missed children. The WG urged the GPEI to make all possible efforts to continue improvement and focus on performance, including the independent assessment of the field operation, detailed investigation of missed children in endemic countries, targeted campaigns for missed children, and improved surveillance.
- In endemic countries with co-circulating WPV and cVDPV, the need to interrupt both WPV and cVDPV2 is critical. However, the WG noted that higher priority should be given to the elimination of cVDPV2 because of the increasing risk of significant type 2 outbreaks due to the increasing size of the cohort of children with no type 2 immunity, following OPV2 withdrawal in April 2016.
- The WG remains concerned about the ongoing IPV shortage and the increasing number of children without any immunity against type 2. The WG urged more countries to consider the adoption of fractional IPV in their routine schedule to mitigate the global supply shortage.
- The WG also recommended that the GPEI reassess its tier classification of countries with respect to prioritization of IPV to take into account the size of the population with no IPV protection, the recent emergences of type 2 events, and the longer-term risks that IPV use could help to mitigate (e.g., iVDPVs, containment failures in countries with PEFs).
- The WG expressed concern over the significant number of PEFs (78 PEFs in 30 countries), and encouraged countries to limit the number of PEFs to the extent possible. The WG further urged the GPEI to put more attention on managing containment risks and the process for the implementation of containment.

Topic 2: Benefit of IPV in eradication, outbreak response and RI

Given the significant IPV shortage, the GPEI should optimize the use of the limited amount of IPV available. In this regard, the WG reviewed different perspectives on the benefit of IPV in 1) achieving WPV1 eradication, 2) outbreak response against cVDPV2, and 3) routine immunization to provide protection to individuals from the risks of iVDPVs and the potential reintroduction of live polioviruses.

The WG reviewed a presentation of epidemiology/vaccinology by Walt Orenstein (Emory University) and a presentation of virology by Mark Pallansch (US CDC). The WG also reviewed poliovirus modelling performed by 3 different modelling groups (Kimberly Thompson (Kid Risk), Nick Grassly (Imperial College), and Guillaume Chabot-Couture (Institute for Disease Modelling).

WPV1 eradication/Outbreak response to cVDPV2

The clinical and epidemiological studies indicate that IPV is very effective in preventing paralysis in vaccine recipients. However, IPV shows limited ability to induce intestinal immunity. Two studies in India showed IPV does reduce the prevalence and duration of faecal shedding following challenges in previously OPV vaccinated children in the study. However, a single dose of IPV administered to children un-primed by a prior dose of OPV containing type 2 has minimal effect on faecal shedding and these children are likely playing the major role in transmission. Nonetheless, one modelling group presented an epidemiological analysis on the incidence of poliomyelitis and poliovirus isolation in environmental samples after campaigns with IPV and OPV in Pakistan and Nigeria indicate a substantial impact, which is significantly greater than that with OPV alone. Mathematical modelling by one modelling group of hypothetical cVDPV2 outbreaks in Pakistan suggests IPV in addition to mOPV2 may give a modest additional increase (up to 5-20%) in intestinal immunity among young children against type 2 that depends on past exposure to type 2 OPV (i.e. geographically heterogeneous). Another modelling group presented a contrasting perspective, showing modelling results of using IPV in addition to OPV compared to using OPV alone for outbreak response for hypothetical cVDPV2 outbreaks in Nigeria and Pakistan that showed minimal benefit of adding IPV for outbreak response because the added IPV does not significantly increase population immunity and is not cost-effective. The WG agreed that mOPV2 campaigns with high coverage should be the priority in response to a cVDPV2. The modelling by one group in Pakistan indicated that the use of IPV may be useful in boosting intestinal immunity in areas outside the mOPV2 use (e.g. areas that the virus is likely to spread, but are not responded by mOPV2), although modeling by another group demonstrated the importance of using enough mOPV in the outbreak response to shut down transmission and showed that in the context of using sufficient amounts of mOPV2 to stop and prevent transmission, the additional use of IPV offers minimal impact and is not cost-effective. A third modelling group showed that when OPV can be used in outbreaks response, either to respond to cVDPV2 outbreaks after OPV2 cessation or in efforts to stop WPV1 circulation, adding a dose of IPV did not significantly improve the mucosal immunity of the target population and adding one more dose of OPV would be equivalent if IPV and OPV campaigns achieved equivalent coverage. However, the coverage of OPV campaigns is likely to be better than that of IPV campaigns given that OPV is distributed house-to-house while IPV is distributed at fixed posts. They also found little difference in the impact of an IPV dose in outbreak response whether the dose was given during the first or last campaign of the outbreak response.

The effect of IPV depends on coverage, OPV status (naive vs. OPV-vaccinated with waning intestinal immunity), OPV take, and adequacy and timing of OPV use. In addition, the WG raised questions about the implications of using IPV in addition to OPV in SIAs on coverage. Giving IPV and OPV at the fixed sites as opposed to the house-to-house, possibly reduces the overall coverage, particularly in the difficult-to-reach populations that vaccinators may already repeatedly miss and that most likely account for most transmission.

Routine immunization

The review of a large body of scientific studies demonstrated that IPV is highly effective in inducing individual protection.

- Multiple studies in a range of settings show nearly 100% seroconversion rates and high antibody titers to all 3 serotypes following 3 doses of IPV
- Some studies show >90% seroconversion rates after 2 doses when initiated after 8 weeks of age (immunogenicity of IPV improves for IPV schedules that avoids interference from maternally-derived antibody)
- Intradermal administration of 2 or 3 fractional doses of IPV provided lower or similar seroconversion rates to the same number of full doses. For example, in a study conducted in Bangladesh, two doses of IPV given intramuscularly at 6 and 14 weeks reported a seroconversion rate of 94.9%, 91%, and 97.5% against types 1, 2, 3 respectively, compared with 87.5%, 80.9% and 88.8% if fractional doses were given intradermally. One study in Cuba reported that three doses of IPV given intramuscularly at 6, 10 and 14 weeks led to seroconversion rates of 89%, 96%, and 99%, compared to 53%, 85%, and 69% for fractional dose IPV given intradermally.
- Two fractional doses of IPV can induce higher seroconversion rates than one full dose of IPV given at a similar age as the first of the fractional doses.

This effect of IPV in individual protection is increasingly important as the world now relies on IPV for type 2 individual immunity in birth cohorts born since the switch. However, there is insufficient evidence that IPV

induces community protection (e.g. mucosal immunity). Some evidence (e.g. India) suggests lower shedding upon reinfection, which may reduce transmission if re-infected individuals account for an important part of the population responsible for transmission. In India, children who received 3 doses of DTP-IPV have a significantly lower rate of poliovirus shedding than in control children (without IPV) 7 days post challenge. Yogyakarta, Indonesia, which introduced IPV relatively early into its routine immunization, did not detect VDPVs after switching from OPV to IPV in 2007. However, the sustained WPV1 transmission among IPV-only vaccinated children in Israel suggests the limited ability of IPV alone in inducing mucosal immunity. Dynamic transmission models show limited benefit of routine immunization with IPV in reducing transmission in most settings (i.e., in places with conditions conducive to relatively high faecal-oral transmission). In this context, the models suggest a relatively higher benefit for IPV in settings with relatively “low force of infection” as opposed to “high force of infection.” The models also demonstrate differences in the relative forces of infection of different types of live polioviruses (OPV, OPV-related viruses, WPV, cVDPV) and the different serotypes, which show the relatively lower transmission potential of parent OPV compared to WPV or cVDPV. The epidemiological experience of no or limited transmission of imported OPV viruses in Israel following its switch from OPV to IPV, but transmission of imported WPV1 demonstrates the importance of the nature of the imported virus. The Israel and Yogyakarta experiences of no generation of cVDPVs from probable imported parent Sabin viruses, which have lower force of infection than existing cVDPVs or WPVs, suggest that high IPV coverage in areas with relatively low fecal-oral transmission may have some impact on prevention the generation of new cVDPVs from imported parent Sabin viruses.

Dynamic transmission modelling for Pakistan and Afghanistan showed that IPV in RI led to very limited benefit in preventing emergence and transmission of cVDPV2, because the issue in this epidemiological block relates to insufficient tOPV use prior to OPV2 cessation to prevent the creation and circulation of cVDPVs.

The models demonstrates small reductions in paralytic incidence because some individual children who received IPV after the switch were not paralyzed by poliovirus infection after the switch. This benefit is clearly related to the coverage achieved with poliovirus vaccines in routine immunisation.

Proposed changes in type 2 outbreak response protocol

As of 9 February 2017, 20 VDPV2 emergences (3 cVDPV, 12 aVDPV, 3 iVDPV and 2 unclassified) have been reported since the switch in May 2016. Countries did not implement outbreak response for 9 events, because detections occurred within 6 mos. from switch, included relatively few NT changes (i.e., suggesting inappropriate continued use of tOPV rather than sustained transmission), and/or the country assessed population immunity as high and the transmission as likely to die out without a response. Fractional IPV was used to respond to one type 2 detection in India that occurred in an area with a high proportion of the population primed with tOPV and good surveillance. SIAs with mOPV2 from the global stockpile have been implemented in Nigeria/Lake Chad and Pakistan, and proposed for Afghanistan and Mozambique and Russia by WHO DG’s Advisory Group for mOPV2 stockpile. Target populations for individual mOPV2 SIAs ranged from 97K (Sokoto rapid response) to 48.2 million doses (Nigeria/Lake Chad).

Based on the 9-month experience since the switch and consideration of the IPV situation, the WHO secretariat proposed a few changes in the type 2 response protocol. Major proposed changes for the next six months include:

- **In response to an unclassified (e.g. ‘new’) VDPV2 or aVDPV2:** Instead of defaulting to an immediate SIA the program proposes no vaccination response (only enhanced investigation and surveillance) unless the event is considered as high risk for further transmission. “High risk” is determined by a composite index of multiple factors in three categories (virology, situational context, and potential for international spread).
- **In response to a cVDPV2:** Instead of the originally proposed 4-5 SIAs, the programme proposes at least 2 ‘high quality’ SIAs with mOPV2 in all outbreak areas and additional SIAs as needed to provide at least 2 ‘high quality’ SIAs (i.e., if prior coverage <80% or evidence exists of persistently missed children or continued transmission). The WG emphasized the importance of both rapid and high quality responses at this stage in the GPEI.
- **Use of IPV:** Consider adding 1 fIPV dose for surrounding high risk populations to boost mucosal immunity in areas outside the scope of mOPV2 response in one SIA only if 1) supply is available; 2) operationally feasible, and 3) mOPV2 SIA coverage not compromised.

- **Scope/target for a mOPV2 response:** Instead of starting with 500k for SIA1 and 2+million for subsequent 3-4 SIAs, the target population should include 2 million for each SIA with the focus on two high-quality SIAs that occur within 14 days of initial sequencing results provided by the GPLN. Additional populations and further extension of the scope of the mOPV2 outbreak response should occur if warranted due to high population mobility or other risk factors.
- **In endemic areas (co-circulating WPV1 and VDPV2):** Prioritize cVDPV2 over WPV1 and proceed as indicated in the type 2 protocol.

The program further proposes to continue current protocol recommendations for other responses (e.g. to iVDPV2, Sabin2, etc) and to update the protocol in areas in which new guidelines have already been endorsed by the GPEI (e.g for general guidance on vaccine management and classification of cVDPVs).

The epidemiology and response experience related to type 2 detections will be re-evaluated over the next 6 months and further revisions proposed as necessary.

WG decisions/recommendations

- The WG re-emphasized that the primary vaccine of choice to eliminate WPVs and respond to cVDPVs is OPV (bOPV1&3 and mOPV2). IPV may offer additional benefit in stopping poliovirus transmission in and around outbreak zones, but current supply constraints require prioritisation of IPV use in RI in countries at risk of VDPV2 emergence and spread (tier 1 and 2)
- The WG agreed that IPV has a significant role in RI in protecting children against poliomyelitis caused by cVDPV2 in countries using bOPV for routine immunization. IPV use is increasingly important as population immunity for type 2 began decreasing at the time of the switch. Access to IPV in RI is important from an equity perspective and therefore, the WG concluded that IPV supply should be prioritized for routine immunization.
- In recognition of the severe global supply constraints for IPV, the WG endorsed the following proposed IPV allocation over the next six months:
 - Prioritize available supply for routine immunization, especially to Tier 1 and 2 countries.
 - No IPV for SIAs in endemic countries or type 2 outbreaks over the next six months
- The WG endorsed the specific proposed changes in type 2 response in principle, noting the following:
 - It is critical to ensure the high quality of SIAs and speed (e.g. within 14 days after detection).
 - Given the expected IPV supply constraints over the next six months and the above prioritization for use of IPV, the reference to IPV use should be taken out of the type2 outbreak response protocol.
 - It is important to identify and address high risk populations during the outbreak and ensure that SIAs reach these populations.
 - The WG encouraged the replenishment of finished vials of mOPV2 to avoid possible stock-out.
 - In endemic countries with co-circulating WPV and cVDPV, the need to interrupt both WPV and cVDPV2 is critical. However, the WG noted that higher priority should be given to the elimination of cVDPV2, because of the increasing risk of significant type 2 outbreaks due to waning type 2 population immunity. Recognizing that simultaneous administration of mOPV and bOPV may be operationally difficult in endemic countries, the WG noted that in situations where both vaccines are required, the two OPVs may be given two weeks (or less if operationally feasible) apart.
- The WG recommended that the Advisory Group of GPEI Eradication and Outbreak Management Group on mOPV2 vaccine provision in response to type 2 poliovirus event or outbreak and/or WHO DG Advisory Group for mOPV2 stockpile should make a recommendation on each new type 2 event, considering specific situations such as population immunity and IPV and mOPV supply.

Topic 3: Discussion on future immunization policy

In October 2016, the SAGE recommended that

- Post-OPV cessation, the immunization schedule should aim to achieve at least 90% seroconversion for individual protection, which will be achieved with at least 2 doses of IPV (either full or fractional)

- Countries will need to continue routine immunization with IPV after the certification of polio eradication for an extended period (e.g. 5, 10 or more years).

SAGE requested the Polio Working Group to make more detailed recommendations (e.g. minimum duration of use of IPV, options for IPV schedule) for the post-OPV immunization schedule to SAGE in April 2017.

The WG reviewed a summary of evidence and WHO secretariat's proposal, status of new OPV/IPV development, future funding policy for IPV through 2021, the availability and cost of different ID devices, and a summary of clinical data on fIPV.

Currently, the programme anticipates OPV withdrawal in 2021 or later, one year after Global Certification Commission (GCC) certification of WPV eradication (i.e. GCC certification minimum 3 years after the last WPV1 case and minimum one year between GCC certification to OPV withdrawal).

Given the uncertain IPV supply, the WHO proposed to make availability of adequate IPV supply a prerequisite for OPV withdrawal. The WHO Secretariat defined an adequate supply as: a) two full doses to Tier 1 countries, b) two fractional doses for all other OPV using countries, and c) a stockpile for outbreak response. 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 $\geq 90\%$ that of 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 WHO Secretariat expects that more than 50% of the birth cohort (e.g. children in relatively high-income countries currently using IPV, and China, India, Indonesia and other countries) will continue using IPV as long as they need to meet the GAP III requirements.

The WHO secretariat proposed that in the post-OPV era, all countries should continue IPV use in the routine immunization for more than 10 years, to ensure durable protection for the long-term and minimize the risks for poliovirus re-emergence from VDPV/WPV emergence (Mathematical modelling and past epidemiology suggested VDPV/WPV types 1 and 3 could potentially emerge 0-4 years after the OPV withdrawal), iVDPVs could excrete for up to 5 years in middle income countries and for 10+ years in high income countries), and containment failure (it could happen even after 10+ years). The recommendation of IPV use for 10+ years should also provide incentives for current producers to stay in the market and for prospective IPV producers to enter the market.

Studies indicated at least two fractional or two full IPV doses (for prime and boost) are required to achieve 90% or more seroconversion (individual protection). However, the first dose should be given after 14 weeks and the interval should be greater than 5 months to optimize seroconversion. Practically, IPV should be given at or after 14 weeks (e.g. with DTP2 or DTP 3) and at or after 9 months (e.g. with measles in most countries). Ideally two full doses IM should be given, but the WHO Secretariat proposes that two fractional doses given in this schedule are fully acceptable.

The WG reviewed the updated estimates of global IPV demand and supply. A two full-dose IPV schedule will require more than 200 million doses in 126 OPV-using countries. The current estimate is that this level of supply (200M) is likely to be available only in 2023-24 primarily from new Sabin IPV suppliers. The WHO Secretariat expects "sufficient supply" of IPV may become available earlier (2021-2022) if some countries adopt a fIPV schedule (assuming demand will be around 150-200 million doses). However, significant uncertainties remain regarding the future IPV supply and national choices between two full and fractional IPV doses, which may result in more than 150 million doses variation in potential annual IPV demand.

The WG also reviewed the future funding policy for IPV. Currently, the GPEI covers the cost of IPV and its introduction in routine immunization into Gavi eligible countries through Gavi and provides subsidies to some non-Gavi countries as well as technical support. The GPEI is likely to continue to support IPV cost in Gavi eligible countries until 2020, either from savings due to the IPV supply shortage and/or new contributions. After 2020, the Gavi Board will need to consider continued support for IPV post-2020 through its own funding. Gavi and the GPEI are discussing post-certification of WPV eradication policy and IPV support for Gavi

supported countries, including future funding and application of Gavi policies on eligibility and co-financing, but did not have resolution of this at the time of the WG meeting.

The Bill & Melinda Gates Foundation (BMGF) is leading the development of new OPV (nOPV) vaccines with improved genetic stability designed to reduce the risks of VAPP and VDPV generation when deployed from a stockpile for outbreak control or re-introduced into routine immunization. Two type 2 nOPV candidates with improved genetic stability and reduced neurovirulence in vitro, and immunogenicity and growth profiles similar to mOPV2, are expected to be in the clinical trials in Belgium in Q2 2017.

The WG reviewed the experience with and availability of different devices to administer vaccine intradermally, including a few alternative intradermal injection devices (e.g. ID adapters, disposable syringe jet injectors) in addition to 0.1 mL auto-disable needle and syringes. Two devices (ID adapter by Helm and Tropis ID jet injector by PharmaJet) have regulatory clearance, with the PharmaJet Tropis device currently under WHO prequalification review and a prequalification specification and verification protocol is being developed for the ID adapter and other needle based ID capable technologies. PATH assessed feasibility and quality of injection with different injection devices. First, it assessed the self-sealing and fragmentation of vial stoppers and confirmed that IPV vial stoppers maintained performance even after multiple (up to 100) piercings with a 27G needle. It also concluded that the dead space varies by brand and model of syringe, but for these devices dead space is very small so that it is possible to administer 5 doses of fIPV with a 1-dose vial (and potentially six doses, due to vial overfill). PATH also reviewed injection quality data and concluded that injection performance measured by bleb size and fluid loss varied between studies, but the clinical relevance of these measures is yet to be established. In the Cuba study, healthcare workers preferred ID jet injectors to needle and syringes, and in the Gambia study found that jet injectors were more acceptable to infants (as determined by crying) as well as parents.

The WG reviewed the updated clinical study data comparing two doses of intradermal fIPV against one full intramuscular IPV dose in terms of seroconversion and type 2 antibody titres. Based on the results of seven studies the WG concluded that two fIPV doses if delivered as well in the field as in the clinical trials are more immunogenic than one full IPV dose. Two fIPV doses are more immunogenic if given four weeks to four months apart and started at or after 14 weeks based on the results of one study.

WG decisions/recommendations

- The WG reiterated that Sabin bOPV should be fully withdrawn from the routine immunization as soon as possible following the GCC certification of global WPV eradication.
- The OPV withdrawal needs to be globally synchronized and planned, and should be possible within 12 to 15 months of certification. The WG noted that the programme will need to ensure sufficient bOPV supplies to support maintaining high population immunity to transmission for serotypes 1 and 3 until coordinated bOPV cessation and develop and maintain mOPV stockpiles, potentially with genetically more stable new OPV if that option becomes available.
- The WG re-confirmed that all countries should continue using at least one dose of IPV after the OPV withdrawal. If IPV supply and funding allows, the WG recommends that countries should adopt a two dose IPV schedule as a preferred option to ensure adequate individual protection against wild or vaccine-derived poliovirus.
- If an OPV-using country is to adopt a two dose IPV schedule after OPV withdrawal, two doses of IPV should be given at or after 14 weeks (e.g. with DTP2 or DTP 3) and at 9-12 months (e.g. with measles). Ideally, two full doses IM should be given, but two fractional doses may provide a similar level of seroconversion based on the results of clinical trials, although no data provide information on the duration of protection (e.g. sufficient antibody) following the receipt of 2 fractional or full IPV doses.
- The WG noted that countries with PEFs should continue the use of IPV as long as required. However, the WG recommended that CAG should review and reconsider the current secondary safeguard requirements in the GAP III as some countries with Sabin facilities have inadequate DTP3 coverage.
- Most WG members agreed that countries, without poliovirus essential facilities, should maintain IPV in their routine immunization schedule for at least 10 years after global OPV withdrawal, to address immediate (VDPVs), intermediate (iVDPV) and longer-term (containment failure and bioterrorism) risks. The recommendation of the use of IPV for 10+ years encourages IPV suppliers to continue IPV supply in the pre and post eradication periods and this ensures the equal protection against the risks

of intentional or unintentional release of poliovirus in the long run. The WG also noted that there is not clear commitment by the donors to support IPV cost. If there is no external funding for IPV available, countries need to prioritize available resources for IPV over other pressing needs. Ideally, all countries would have access to IPV-containing hexavalent vaccine and willingness-to-pay for this vaccine out of their national budgets for use in their routine programmes.

- One WG member disagreed and indicated that existing economic analyses only support a recommendation to continue IPV immunization for minimum 5 years in all countries after the OPV withdrawal. The WG member noted that the long-term risks faced by countries will differ such that the relative benefits of IPV use would differ in the long-term (with relatively high-income countries benefitting more from IPV due to increased risks from iVDPVs and PEFs), and that application of a uniform recommendation does not account for the differences in risks, benefits, or the long-term willingness-to-pay for IPV. The WG member also emphasized the importance of considering the opportunity costs associated with requiring continued spending for long-term use of IPV given the cost-effectiveness and other competing investments in public health.
- The WG recommended that countries ensure optimal use of bOPV prior to bOPV withdrawal in order to ensure the highest possible population immunity against type 1 and 3 at the time of the withdrawal and asked the Secretariat to ensure that its bOPV SIA calendar and ordering for bOPV reflect this recommendation and to provide projections about OPV supply as OPV manufacturers make plans to sunset OPV production.

Summary and next steps for the SAGE Working Group

The results of the WG will be presented at the April SAGE meeting for further discussions. The Secretariat and WG will also prepare and complete “evidence to decision” tables for the review by the SAGE.

In addition, the WG will continue to provide technical oversight on major areas, such as:

- Progress towards elimination of WPV and cVDPV
- Polio vaccine supply issues (both IPV and OPV)
- Risk mitigation strategy before the OPV cessation (e.g. bOPV campaigns before the cessation, detection of iVDPV cases)
- Update on iVDPV epidemiology and development of antiviral drugs
- Remaining issues in future immunization policy

SAGE evidence to recommendations framework

<p>Question: Should countries continue IPV vaccination in their routine immunization programme after the certification of polio eradication? If so, what is the optimum schedule and for how long should countries continue?</p> <p>Population: Newborn children (esp. those in currently OPV-using countries)</p> <p>Intervention: Vaccination (One or two doses of inactivated poliovirus vaccine; IPV)</p> <p>Comparison(s): No vaccination</p> <p>Outcome: Prevention of poliomyelitis, possibly caused by vaccine-derived poliovirus (VDPV) or intentional and unintentional release of poliovirus from polio-essential facilities (PEFs)</p> <p>Background: The Oral Poliovirus Vaccine (OPV) offers safe and effective lifelong protection for humans against polio paralysis. Over the past ten years, more than 10 billion doses of OPV have been given to nearly three billion children worldwide. However, on rare occasions, giving OPV can result in cases of polio due to vaccine-associated paralytic polio (VAPP) in fully susceptible individuals (approximately 1 in 2.7 million doses of OPV) and OPV use in populations with insufficient coverage can allow ongoing transmission of OPV-related viruses that can lose their attenuating mutations and cause outbreaks of circulating vaccine-derived polioviruses (cVDPVs). For this reason, the global eradication of polio requires the cessation of all OPV in routine and supplementary immunization, as soon as possible after the eradication of wild poliovirus (WPV) transmission. In late-April-early May 2016, all OPV-using countries switched from trivalent OPV to bivalent OPV to minimize the risks associated with type 2 cVDPV, and most countries introduced at least one dose of IPV in their routine immunization prior to the switch.</p> <p>Anticipating the global certification of serotype 1 and 3 wild poliovirus eradication in near future, SAGE requested the Polio WG to discuss and propose a post-OPV immunization policy.</p>				
	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	No <input type="checkbox"/> Uncertain <input type="checkbox"/> Yes <input checked="" type="checkbox"/> Varies by setting <input type="checkbox"/>	In May 2014, WHO Director General declared that international spread of poliovirus as Public Health Emergency of International Concern (PHEIC). The public health significance will be even higher, if poliovirus spreads after the global	1

			certification of polio eradication	
BENEFITS & HARMS OF THE OPTIONS	<p><u>Benefits of the intervention</u></p> <p>Are the desirable anticipated effects large?</p>	<p>No <input type="checkbox"/></p> <p>Uncertain <input type="checkbox"/></p> <p>Yes <input type="checkbox"/></p> <p>Varies <input checked="" type="checkbox"/></p>	<p>Risk of poliovirus circulation after the global OPV cessation.</p> <p>The risk of poliovirus re-emergence and circulation continues as long as live polioviruses exist, however, the risks change with time and they can be managed. Mathematical modelling and past epidemiology suggested VDPV/WPV types 1 and 3 could potentially emerge 0-4 years after the OPV withdrawal, with this risk depending in large part on management of population immunity prior to and just before coordinated global cessation of bOPV, outbreak response capacity and actions, and surveillance quality. The current epidemiology indicates that iVDPVs could excrete for up to 5 years in middle income countries and for 10+ years in high income countries. Lastly, containment failure or unintentional release of poliovirus from a polio essential facility (e.g. vaccine production or research facility) could happen anytime, even after 10 years, and</p>	

			<p>bioterrorism represents a potential threat.</p> <p>Effectiveness of IPV</p> <p>A significant body of evidence shows that one or two doses of full or fractional IPV can induce individual protection against poliovirus. Studies indicate at least two fractional or two full IPV doses (for prime and boost) are required to achieve 90% or more seroconversion (individual protection). Available evidence suggests the seroconversion is optimized if the first IPV dose should be given at 14 weeks or later and the interval between this and the second dose should be greater than 4 months (See separate table and figure on immunogenicity).</p> <p>There is no direct data on the duration of protection (e.g. sufficient antibody) following the receipt of 2 fractional or full IPV doses. However, there is no evidence which suggests that there is waning immunity against polioviruses. Although antibody decline over time, and may fall</p>	
--	--	--	---	--

			<p>below detectable levels, in no instance such decreases increased susceptibility to poliomyelitis (paralytic disease) or led to outbreaks of poliovirus.</p> <p>The role of IPV with respect to community protection remains more mixed. Some evidence (e.g. India) suggests lower shedding of an IPV-protected individual upon re-exposure with a live poliovirus, which may reduce transmission if re-infected individuals account for an important part of the population responsible for transmission. In India, individual children who received 3 doses of DTP-IPV have a significantly lower rate of poliovirus shedding than in control children (without IPV) 7 days post challenge. Yogyakarta, Indonesia, which introduced IPV relatively early into its routine immunization, did not detect VDPVs after switching from OPV to IPV in 2007. However, the sustained WPV1 transmission among IPV-only vaccinated children in Israel, despite high coverage with IPV, suggests the limited ability of IPV alone in inducing mucosal immunity and</p>	
--	--	--	---	--

			preventing transmission in a population. Dynamic transmission models show limited benefit of routine immunization with IPV in reducing transmission in low-income settings (i.e., in places with conditions conducive to relatively high faecal-oral transmission).	
<u>Harms of the intervention</u>	No <input type="checkbox"/> Uncertain <input type="checkbox"/> Yes <input checked="" type="checkbox"/> Varies <input type="checkbox"/>		Numerous studies suggest that IPV is safe to administer.	
Are the undesirable anticipated effects small?				
Balance between benefits and harms	Favours intervention <input checked="" type="checkbox"/> Favours comparison <input type="checkbox"/> Favours both <input type="checkbox"/> Favours neither <input type="checkbox"/> Unclear <input type="checkbox"/>		On the individual level, benefit of protection from poliomyelitis related disease outweighs any adverse effect of vaccination (e.g. pain during immunization, AEFIs).	
What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention No included studies <input type="checkbox"/> Very low <input type="checkbox"/> Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input checked="" type="checkbox"/> Safety of the intervention No included studies <input type="checkbox"/> Very low <input type="checkbox"/> Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input checked="" type="checkbox"/>		A large body of evidence supports individual effectiveness (see the WHO GRADE Table) and safety of IPV (see the GACVS Report) http://www.who.int/immunization/polio_grad_ipv_effectiveness.pdf?ua=1 http://www.who.int/vaccine_safety/committee/reports/wer8907.pdf?ua=1	

VALUES & PREFERENCES	<p>Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?</p>	<p>No <input type="checkbox"/> Probably No <input type="checkbox"/> Uncertain <input type="checkbox"/> Probably Yes <input checked="" type="checkbox"/> Yes <input type="checkbox"/> Varies <input type="checkbox"/></p>	<p>No evidence was retrieved on the values and preferences or the variability of these at the national level. On the individual level, avoidance of poliomyelitis related disease would likely outweigh any adverse effect of vaccination (pain during immunization, AEFIs). Economic modelling related to this topic suggests that countries will face different risks of potential reintroduction of polioviruses over time, with those countries that include polio essential facilities, providing long-term, high-quality supportive care for IVDPVs, and/or expressing greater concern about bioterrorism (i.e., relatively higher income countries) likely to place more value on the insurance provided by long-term IPV immunization than countries that face lower risks and/or remain less concerned about desiring insurance from bioterrorism.</p>	<p>At the same time, it is important to advocate for the value of continued immunization against poliovirus after the global certification, in order to ensure community acceptance and population immunity.</p>
RESOURCE USE	<p>Are the resources required small?</p>	<p>No <input checked="" type="checkbox"/> Uncertain <input type="checkbox"/> Yes <input type="checkbox"/> Varies <input type="checkbox"/></p>	<p>The current range of IPV price for UNICEF market is about 1-3 USD per dose. If a country adopts a fractional dose IPV schedule, the expected cost of the vaccine per child per dose is significantly</p>	<p>There is an opportunity cost associated with continued long-term use of IPV given other competing investments in public health, especially if the dedicated external funding for</p>

		<p data-bbox="389 1671 448 1823">Cost-effectiveness</p> <p data-bbox="405 1541 459 1563">No <input type="checkbox"/></p> <p data-bbox="405 1384 459 1442">Uncertain <input type="checkbox"/></p> <p data-bbox="405 1263 459 1285">Yes <input type="checkbox"/></p> <p data-bbox="405 1182 459 1227">Varies <input checked="" type="checkbox"/></p>	<p data-bbox="268 1039 293 1115">lower.</p> <p data-bbox="389 712 1054 1115">The only published cost-effectiveness analysis supports the recommendation that all countries should continue at least one dose of IPV immunization in their national program for a minimum of 5 years after coordinated bOPV withdrawal. The analysis reported less favourable economics for a policy recommendation of a minimum of 10 years of IPV use in all countries after coordinated bOPV cessation. The majority of Polio WG members preferred a recommendation of IPV use for a minimum of 10 years to ensure protection against the risks of intentional or unintentional release of poliovirus in the long run.</p>	<p data-bbox="268 456 293 689">IPV is not available.</p> <p data-bbox="389 309 1118 689">One Polio WG member stated the recommendation should be consistent with the best strategy identified in the cost-effectiveness analysis (i.e., a minimum of 5 years of including at least one dose of IPV use in all countries) after coordinated bOPV cessation. The member emphasized that any country could choose to include IPV in its national immunization program for longer (and emphasized an expectation that relatively higher income countries would do so given their relative risks and benefits), but emphasize that application of a uniform recommendation does not account for the differences in risks, benefits, or the long-term willingness-to-pay for IPV.</p>
--	--	--	--	---

EQUITY	<p>What would be the impact on health inequities?</p>	<p>Increased <input checked="" type="checkbox"/></p> <p>Uncertain <input type="checkbox"/></p> <p>Reduced <input type="checkbox"/></p> <p>Varies <input type="checkbox"/></p>	<p>It is important to ensure protection in all populations (especially in developing countries) from an equity perspective as most high-income countries have already introduced more than 3 doses of IPV into their routine immunization schedule</p>	<p>One Polio WG member noted that requiring countries to pay for IPV could lead to opportunity costs that would shift resources away from more cost-effective non-polio interventions, and thus, while recommending IPV increases equity related to protection from poliomyelitis, it could at least theoretically reduce overall equity with respect to protection from infectious diseases or overall health</p>
--------	---	---	--	--

ACCEPTABILITY	<p>Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?</p>	<p style="text-align: center;"> <input checked="" type="checkbox"/> <i>Intervention</i> <input type="checkbox"/> <i>Comparison</i> <input type="checkbox"/> <i>Both</i> <input type="checkbox"/> <i>Neither</i> <input type="checkbox"/> <i>Unclear</i> </p>	<p>The previous SAGE recommendation to introduce one IPV dose into the routine immunization was adopted by all countries, so the recommendation of an additional dose of IPV should be acceptable as a policy, given the sufficient funding is available.</p> <p>However, at this point, there is not clear commitment from the donor community to support IPV after OPV cessation (since the recommendation would become effective only in 2021 or later).</p> <p>If there is no external funding for IPV, countries would need to prioritize available resources for IPV over other pressing needs.</p> <p>It is presumed that the use of one or two doses of IPV would be acceptable to the target group if no additional visit at the health clinic is needed and the costs are covered by the health care provider.</p>	<p>One Polio WG member suggested that costs of IPV remain an issue for countries and that further work on the cost-effectiveness of the 2-dose IPV schedule appear warranted, although going from a 1 full IPV dose schedule to a 2 fractional IPV dose schedule could provide significant cost savings. This WG member indicated an expectation that some countries would probably not prioritize scarce resources for IPV in the context of competing priorities.</p>
<p>Which option is acceptable to target group?</p>	<p style="text-align: center;"> <input checked="" type="checkbox"/> <i>Intervention</i> <input type="checkbox"/> <i>Comparison</i> <input type="checkbox"/> <i>Both</i> <input type="checkbox"/> <i>Neither</i> <input type="checkbox"/> <i>Unclear</i> </p>	<p>It is presumed that the use of one or two doses of IPV would be acceptable to the target group if no additional visit at the health clinic is needed and the costs are covered by the health care provider.</p>		

FEASIBILITY	Is the intervention feasible to implement?	<p>No <input type="checkbox"/> Probably No <input type="checkbox"/> Uncertain <input type="checkbox"/> Probably Yes <input type="checkbox"/> Yes <input checked="" type="checkbox"/> Varies <input type="checkbox"/></p>	<p>The intervention is feasible as it does not require additional visits. However, current IPV supply remains highly limited, such that some countries that planned to introduce IPV had to delay their introduction. There is a risk of IPV shortage continuing into the long-term, especially if the market after the global cessation is limited. The recommendation of the use of IPV for 10+ years should encourage vaccine suppliers to continue IPV supply in the pre and post eradication periods.</p>		
Balance of consequences	Undesirable consequences <i>clearly outweigh</i> desirable consequences in most settings <input type="checkbox"/>	Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings <input type="checkbox"/>	The balance between desirable and undesirable consequences is <i>closely balanced or uncertain</i> <input type="checkbox"/>	Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings <input type="checkbox"/>	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings <input checked="" type="checkbox"/>
Type of recommendation	We recommend the intervention <input checked="" type="checkbox"/>	We suggest considering recommendation of the intervention <input type="checkbox"/> Only in the context of rigorous research <input type="checkbox"/> Only with targeted monitoring and evaluation <input type="checkbox"/> Only in specific contexts or specific (sub)populations		We recommend the comparison <input type="checkbox"/>	We recommend against the intervention and the comparison <input type="checkbox"/>

<p>Recommendation (text)</p>	<ul style="list-style-type: none"> • All countries should expect to continue using at least one dose of IPV after the coordinated bOPV withdrawal. If IPV supply and funding allows, the WG recommends that countries should adopt a two dose IPV schedule as a preferred option to ensure adequate individual protection against potential reintroduction of wild or vaccine-derived poliovirus. • If an OPV-using country is to adopt a two dose IPV schedule after bOPV withdrawal, two doses of IPV should be given at or after 14 weeks (e.g. with the 2nd or 3rd dose of DTP-containing vaccine) and at 9-12 months (e.g. with measles). Ideally, two full doses IM should be given, but two fractional doses may provide a similar level of seroconversion based on the available results of clinical trials, although no data provide information on the duration of protection (e.g. sufficient antibody) following the receipt of 2 fractional or full IPV doses. • Countries with Poliovirus Essential Facilities (PEFs) should continue the use of IPV as long as mandated by Global Action Plan (GAP III). However, countries, without PEFs should maintain IPV in their routine immunization schedule for at least 10 years after global OPV withdrawal, to address immediate (VDPVs), intermediate (iVDPV) and longer-term (containment failure and bioterrorism) risks. If there is no external funding for IPV available, countries need to decide how to prioritize available resources given other pressing public health needs. • WHO should review the secondary safeguard requirements in the Global Action Plan (GAP III) to ensure adequate protection in countries with PEFs
<p>Implementation considerations</p>	<p>Recommendations will be made available in the standard WHO format (WHO position paper). As mentioned above, the implementation of recommendation is contingent on availability of sufficient IPV and external funding support.</p>
<p>Monitoring and evaluation</p>	<p>It is important to continue monitoring of immunization coverage and sustain disease surveillance even after the global certification of polio eradication.</p>

<p>Research priorities</p>	<p>Further research is recommended for</p> <ul style="list-style-type: none"> • More information about immunogenicity and feasibility of two full-dose and fractional doses administered at time of 3rd dose of DTP-containing vaccine and measles or other schedules (ongoing) • Long-term duration of protection induced by fractional dose IPV
----------------------------	---

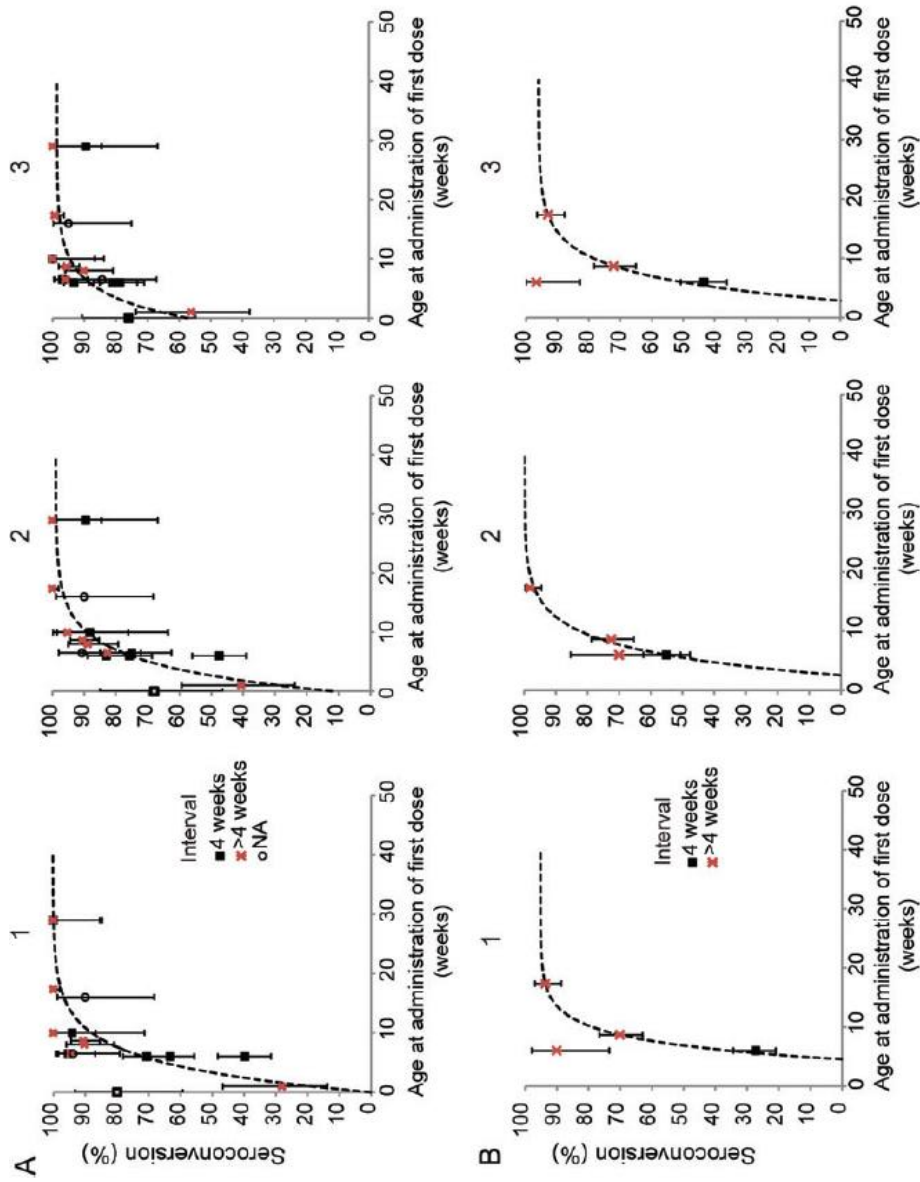
Seroconversion rates following 1–3 doses of inactivated poliovirus vaccine (IPV) in different routine immunization schedules						
Author year (Ref.)	Country	Schedule	N	Type 1	Type 2	Type 3
Intramuscular administration of 1 dose						
McBean 88 [45]	US	2 mo	309	42%	35%	54%
Simasathien 94 [46]	Thailand	2 mo	103	25%	39%	28%
Resik 10 [40*]	Cuba	6 wk	177	19%	36%	42%
Mohammed 10 [47*]	Oman	2 mo	186 ^b	22%	32%	45%
Resik 13 [39**]	Cuba	4 mo	153	46%	63%	32%
Intramuscular administration of 2 doses						
WHO 97 [48]	Oman	6, 10 wk	136	71%	83%	81%
WHO 97 [48]	Thailand	6, 10 wk	141	40%	48%	79%
Cuba IPV group 05 [27]	Cuba	8, 16 wk	72	90%	89%	90%
Resik 10 [40*]	Cuba	6, 10 wk	177	63%	76%	93%
Mohammed 10 [47*]	Oman	2, 4 mo	186 ^b	91%	91%	96%
Resik 13 [39**]	Cuba	4, 8 mo	153	100%	100%	99%
Intramuscular administration of 3 doses						
McBean 88 [45]	US	2, 4, 18 mo	219	99%	100%	100%
Simasathien 94 [46]	Thailand	2, 4, 6 mo	92	96%	95%	98%
WHO 97 [48]	Oman	6, 10, 14 wk	136	90%	96%	95%
WHO 97 [48]	Thailand	6, 10, 14 wk	141	67%	65%	94%
Dayan 05 [49]	P. Rico	6, 10, 14 wk	225	86%	86%	97%
Dayan 05 [49]	P. Rico	2, 4, 6 mo	230	100%	100%	99%
Cuba IPV Group 05 [27]	Cuba	6, 10, 14 wk	52	94%	83%	100%
Resik 10 [40*]	Cuba	6, 10, 14 wk	177	89%	96%	99%
Mohammed 10 [47*]	Oman	2, 4, 6 mo	186 ^b	100%	100%	100%
Cadorna-Carlos 12 [50]	Philippines	6, 10, 14 wk	115	98%	98%	100%
Intradermal administration of 1–3 fractional doses						
Resik 10 [40*]	Cuba	6 wk	187	5%	19%	8%
Resik 10 [40*]	Cuba	6, 10 wk	187	21%	55%	43%
Resik 10 [40*]	Cuba	6, 10, 14 wk	187	53%	85%	69%
Mohammed 10 [47*]	Oman	2 mo	187 ^b	10%	17%	9%
Mohammed 10 [47*]	Oman	2, 4 mo	187 ^b	70%	72%	72%
Mohammed 10 [47*]	Oman	2, 4, 6 mo	187 ^b	97%	96%	98%
Cadorna-Carlos 12 [50]	Philippines	6, 10, 14 wk	115	99%	95%	95%
Resik 13 [39**]	Cuba	4 mo	157	17%	47%	15%
Resik 13 [39**]	Cuba	4, 8 mo	157	94%	98%	93%

^a Cumulative seroconversion rates defined as children with antibody concentrations ≥ 4 -fold the expected value based upon decline from baseline levels.

^b Denominators varied for each serotype. Included studies conducted with enhanced IPV, with a sample size ≥ 50 and that provided information on seroconversion rates.

Source: Estivariz C, et al. *Current Opinions in Virology* 2013;3:309-315.

Figure 1: Proportion of children seroconverting to each serotype after 2 doses of IPV (A: Full-dose, B: Fractional dose)



Source: Grassly NC. J Infect Dis 2014; 210 Suppl 1: S439-46

Immunogenicity and Effectiveness of Routine Immunization With 1 or 2 Doses of Inactivated Poliovirus Vaccine: Systematic Review and Meta-analysis

Nicholas C. Grassly

Department of Infectious Disease Epidemiology, St Mary's Hospital Medical School, Imperial College London, United Kingdom

Background. The World Health Organization has recommended that all 124 countries currently using only oral poliovirus vaccine (OPV) introduce at least 1 dose of inactivated poliovirus vaccine (IPV) before the global withdrawal of serotype 2 OPV in 2016. A 1- or 2-dose schedule, potentially administered intradermally with reduced antigen content, may make this affordable.

Methods. A systematic review and meta-analysis of studies documenting seroconversion after 1 or 2, full or fractional (1/5) doses of enhanced-potency IPV was performed. Studies reporting the clinical efficacy of IPV were also reviewed.

Results. Twenty study arms from 12 published articles were included in the analysis of seroconversion. One full dose of intramuscular IPV seroconverted 33%, 41%, and 47% of infants against serotypes 1, 2, and 3 on average, whereas 2 full doses seroconverted 79%, 80%, and 90%, respectively. Seroconversion increased with age at administration. Limited data from case-control studies indicate clinical efficacy equivalent to the proportion seroconverting. One fractional dose of intradermal IPV gave lower seroconversion (10%–40%), but after 2 doses seroconversion was comparable to that with full-dose IPV.

Conclusions. Routine immunization with 2 full or fractional doses of IPV given after 10 weeks of age is likely to protect >80% of recipients against poliomyelitis if poliovirus reemerges after withdrawal of OPV serotypes.

Keywords. inactivated poliovirus vaccine; IPV; poliomyelitis; immunogenicity; seroconversion; efficacy; eradication; endgame; antibody.

The Global Polio Eradication Initiative (GPEI) Strategic Plan for 2013–2018 envisages globally coordinated withdrawal of the live oral poliovirus vaccine (OPV), based on the long-recognized need to prevent the emergence and spread of vaccine-derived polioviruses [1, 2]. Withdrawal will happen serotype by serotype, starting with serotype 2 OPV (OPV2) by mid-2016,

given the global elimination of this serotype of wild poliovirus (the last naturally occurring case was reported in India in 1999). Routine immunization programs will therefore replace trivalent OPV with serotype 1 and 3 bivalent OPV, and serotype 2–containing OPV will no longer be used during supplementary immunization activities. Subsequent withdrawal of serotypes 1 and 3 will follow, contingent on the certified elimination of transmission of these serotypes, such that OPV will no longer be used as of 2019.

Global withdrawal of OPV will put the 124 countries currently using a trivalent OPV schedule at risk of outbreaks of poliomyelitis should poliovirus be reintroduced. In November 2012, the World Health Organization Strategic Advisory Group of Experts (SAGE) on Immunization therefore recommended that “all countries should introduce at least 1 dose of IPV in their

Correspondence: Nicholas C. Grassly, DPhil, Department of Infectious Disease Epidemiology, St Mary's Hospital Medical School, Imperial College London, Norfolk Place, London W2 1PG, UK (n.grassly@imperial.ac.uk).

The Journal of Infectious Diseases® 2014;210(S1):S439–446

© The Author 2014. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

DOI: 10.1093/infdis/jit601

routine immunization schedules to mitigate the risks associated with the withdrawal of OPV2” [3]. Individuals vaccinated with IPV would be protected against poliomyelitis in the event of an outbreak of vaccine-derived or wild-type poliovirus. A degree of herd immunity would also be provided by this vaccine, thereby limiting transmission of any reintroduced or reemergent poliovirus. Following withdrawal of OPV2, but before complete OPV cessation, IPV may provide additional benefits in terms of boosting immunity to serotypes 1 and 3, which could help wild poliovirus eradication, and preventing vaccine-associated paralytic poliomyelitis (VAPP) in any seronegative individuals subsequently vaccinated with bivalent or monovalent OPV.

A prerequisite for the universal adoption of IPV in routine immunization is the availability of an affordable product [3]. The higher cost of manufacture and limited market volume has meant that the price of stand-alone IPV is at least 10 times that of OPV. Even with a larger market volume, the price of stand-alone IPV is unlikely to drop much below US \$1 per dose [4]. For this reason, the GPEI is supporting multiple strategies for reduced-cost IPV, including evaluation of 1- or 2-dose schedules, licensing of products with a reduced antigen content based on intradermal delivery or the use of adjuvants, and pursuit of cheaper production costs by using safer vaccine seed strains including Sabin or further attenuated polioviruses (IPV manufacture is traditionally based on inactivation of wild-type strains). Over the timeframe envisaged for serotype 2 OPV withdrawal, currently licensed stand-alone IPV is likely to meet most of the demand from countries currently using trivalent OPV. The budget for the GPEI Strategic Plan therefore includes funds to support the universal introduction of 1 dose of IPV to routine immunization schedules. Intradermal delivery of a fractional (1/5) dose may also be an option if regulatory approval can be obtained for a label change to include intradermal delivery from a multidose vial. A reduced-antigen-content, alum-adjuvanted product may also be achievable in the medium term depending on licensing and regulatory approval [1]. Multivalent vaccines containing IPV may be an option for some countries, and in the longer term these vaccines may meet demand for polio immunization in middle and low-income countries. However, current pricing of these products, limited production capacity, the absence of a hexavalent product containing whole cell pertussis, and the need for 3 doses means that these products are unlikely to be an option in the medium term [4].

In the short term, countries currently using trivalent OPV will need to make a decision on the most appropriate IPV schedule and product. The evidence base for this decision is limited in the case of 1- or 2-dose schedules, as most studies have focused on immunization with at least 3 doses of IPV. A single dose of IPV can prime individuals for a subsequent booster in the event of an outbreak. It may also protect against poliomyelitis and poliovirus transmission, although the relationship

between priming and vaccine efficacy is not well understood [5]. In this article, I review the immunogenicity and effectiveness of 1- and 2-dose IPV schedules given as a stand-alone or combination product, at full or reduced antigen content via the intramuscular or intradermal route to healthy children. I do not consider >2-dose schedules, as there is an ample evidence base and experience with their use [6, 7]. This article is therefore intended as a resource to decision makers considering the different policy options for the introduction of IPV to routine immunization before the global withdrawal of OPV serotypes that is planned to commence in 2016.

SEROCONVERSION DATA

Studies reporting seroconversion after 1 or 2 full or fractional (1/5) doses of IPV were identified through a systematic review of published studies. The protocol for this review is described in the [Supplementary Methods](#). A total of 20 independent study arms were identified in 12 published articles after screening 958 articles returned by a search of the Web of Knowledge collection of databases ([Supplementary Figure 1](#)).

Single Dose

Seven studies were identified that reported seroconversion after a single dose of enhanced potency IPV given by intramuscular injection. These 7 studies included results from a total of 8 independent study arms ([Supplementary Table 1](#)). The overall proportion of children seroconverting after a single dose was 33%, 41%, and 47% for serotypes 1, 2, and 3 respectively, although there was significant heterogeneity among studies (χ^2 test for heterogeneity, $P < .001$ for all 3 serotypes). In particular, the proportion seroconverting was strongly dependent on the age at administration for serotypes 1 and 2, ranging from 8%–15% when given 1 week after birth, to 46%–63% when given at 4 months of age (Figure 1). This trend was less apparent for serotype 3, with a nonsignificant, negative linear trend with age at administration, although this was because of a single study with poor serotype 3 immunogenicity of IPV given at 4 months of age [9].

Three studies reported seroconversion after a single fractional (1/5) dose of enhanced potency IPV administered via the intradermal route, all using a needle-free device (Biojector 2000, Bioject Medical Technologies). The overall proportion of children showing seroconversion was 10%, 27%, and 10% for serotypes 1, 2, and 3 respectively, significantly lower than that observed after the full-dose product administered intramuscularly (mixed-effects binomial regression $P < .001$ for all 3 serotypes; Figure 1, [Supplementary Table 1](#)). In all 3 studies the geometric mean titer (GMT) of poliovirus serum neutralizing antibodies was lower after a single fractional dose of intradermal IPV compared with children who received a full dose intramuscularly [9–11].

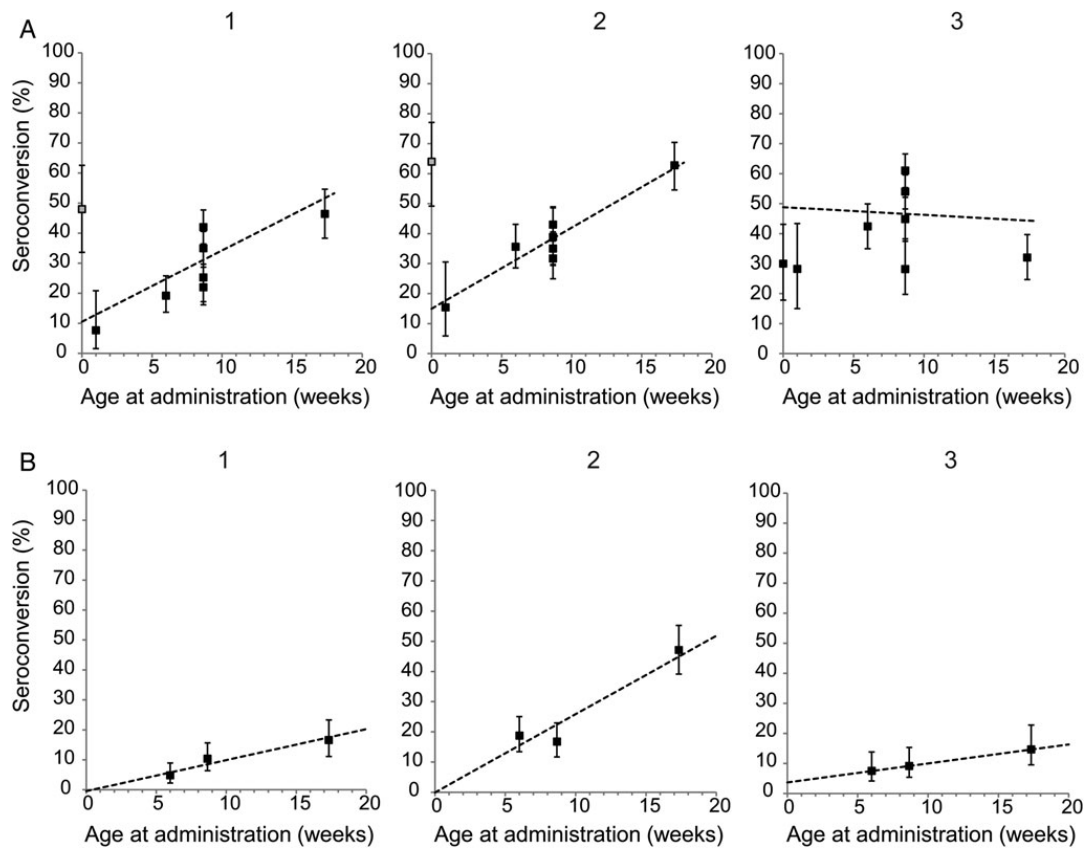


Figure 1. Proportion of children seroconverting to each serotype after 1 dose of inactivated poliovirus vaccine (IPV), plotted against age at administration. *A*, Full-potency IPV given intramuscularly. *B*, Fractional (1/5) dose IPV given intradermally using a needle-free device. The dashed line shows the maximum-likelihood linear trend (likelihood ratio test for trend $P < .001$, $< .001$, and $.49$ for serotypes 1, 2, and 3 in *A*, and $P < .001$, $< .001$, and $.027$, respectively, in *B*). The error bars show the 95% confidence intervals for the data. Seroconversion was defined in each study as either a 4-fold rise in neutralizing antibody titer compared with that expected based on the expected decline in maternal antibodies, or detection of neutralizing antibodies in children previously seronegative (see [Supplementary Table 1](#) for details for each study). Seroconversion data from a study of IPV given at birth in India is shown with a gray fill for serotypes 1 and 2 (*A*), as a high proportion of infants showed seroconversion to these serotypes in the control arm of the study where IPV was not administered at birth [8]. Data from this study for serotypes 1 and 2 were therefore not included when estimating the best-fit linear trend.

Two Doses

Ten articles were identified that reported seroconversion after 2 doses of enhanced-potency IPV given by intramuscular injection in a total of 16 independent study arms. The overall proportion of children seroconverting after 2 doses was 79%, 80%, and 90% for serotypes 1, 2, and 3 respectively, with significant heterogeneity among studies (χ^2 test for heterogeneity, $P < .001$ for all 3 serotypes; [Supplementary Table 2](#)). Seroconversion increased with age at which the first dose was administered, with most studies showing at least 80% seroconversion for each serotype when the first dose was given at 10 weeks after birth or later (Figure 2). An interval of 4 weeks between the first and second dose was associated with a lower proportion of children seroconverting compared with longer intervals between doses (average seroconversion of 65%, 71%, and 87% for 4-week interval compared with 90%, 89%, and 93% for a longer interval—

on average 9 weeks—for serotypes 1, 2, and 3 respectively, although this was nonsignificant based on mixed-effects binomial regression, $P = .56$, $.084$, and $.59$ for serotypes 1, 2, and 3, respectively).

Four studies reported seroconversion after 2 fractional (1/5) doses of enhanced potency IPV administered via the intradermal route using either a needle and syringe or needle-free device. The proportion of children showing seroconversion was 63%, 74%, and 70% on average for serotypes 1, 2, and 3, respectively, which was significantly lower than that observed after the full-dose product was administered intramuscularly (mixed-effects binomial regression, $P < .001$ for all 3 serotypes; [Supplementary Table 2](#)). However, even for this limited sample size, seroconversion appeared dependent on the age at administration of the first dose and the interval between the doses (Figure 2). Excluding the single study that administered a

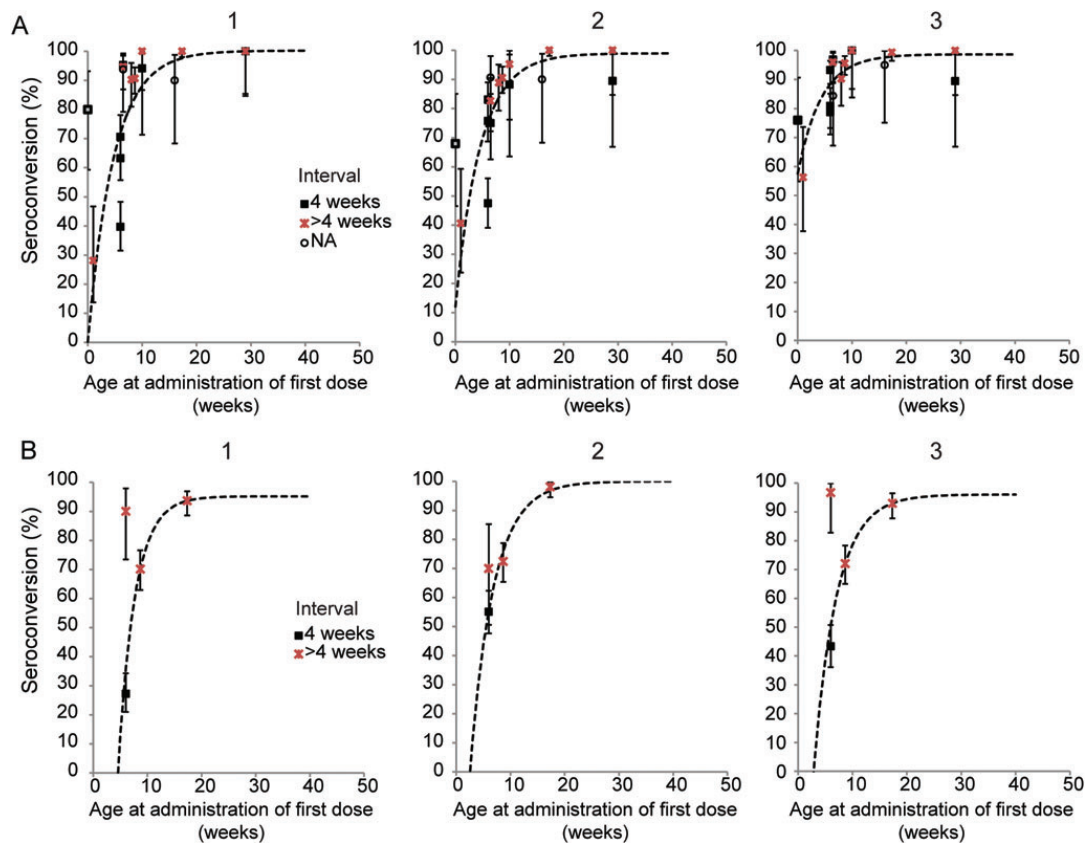


Figure 2. Proportion of children seroconverting to each serotype after 2 doses of inactivated poliovirus vaccine (IPV), plotted against age at administration of the first dose. *A*, Full-potency IPV given intramuscularly. *B*, Fractional (1/5) dose IPV given intradermally using a needle and syringe or needle-free device. The legend indicates the interval between the doses, and the error bars the 95% confidence intervals. The dashed line indicates the trend in seroconversion with age at administration of the first dose based on an exponential curve with intercept and asymptote estimated from the data using maximum likelihood. The asymptote was constrained to be $\leq 100\%$. Seroconversion is defined as in Figure 1 (see [Supplementary Table 2](#) for details for each study). Data from the study in India with significant seroconversion to serotypes 1 and 2 in the control arm are shown in gray as for Figure 1 and excluded from the maximum likelihood curve fit [8].

fractional dose of IPV at 6 and 10 weeks [11] increased the average seroconversion to 82%, 83%, and 83% for serotypes 1, 2, and 3, respectively. Nonetheless, after 2 doses the GMT of poliovirus-specific serum neutralizing antibodies remained lower among children receiving fractional-dose intradermal IPV compared with full-dose product intramuscularly in all studies that directly compared these products—and this difference persisted even after 3 doses [9–11].

PRIMING

Serum neutralizing antibodies are thought to be the major determinant of protection against poliomyelitis, although cellular immunity also plays a role [12]. The protective effect of antibody was determined during early attempts to prevent poliomyelitis through the administration of gamma globulin [13]. Seroconversion is therefore the standard measure of protective

immunity against poliomyelitis following immunization with IPV. However, it has also been argued that even in the absence of detectable antibody, immunological memory following administration of IPV may be sufficient to protect against poliomyelitis [5, 14].

Recent data from Cuba suggest that immunological priming develops in the majority (at least 90%) of children following immunization with a single full intramuscular or fractional (1/5) intradermal dose of IPV given at 4 months of age, despite more limited seroconversion (range, 17%–63% depending on serotype and route of administration; [9]). In this study, priming was evidenced by rapid seroconversion, 7 days after administration of a subsequent dose of IPV at 8 months of age. A similar anamnestic response was documented in at least 80% of infants immunized with full-dose IPV at birth, when given a booster dose at 6 months of age or older [15]. Earlier studies also provided evidence for priming in the majority of children

when immunized with different IPV preparations at 5 months of age [16].

IMMUNE MEMORY

After 3 or 4 doses of IPV, including a booster dose in the second year of life, serum neutralizing antibodies to poliovirus remain at a detectable level in the majority of recipients for many years [6]. The titer of neutralizing antibody drops quite steeply—by approximately 10- to 100-fold—in the first 2 years after vaccination, but then declines more slowly in the subsequent decade [17, 18]. Even in the absence of detectable antibodies, an anamnestic response to a booster dose can be observed at least 8 years after a primary immunization series with IPV [19]. Furthermore, in elderly individuals born before routine immunization against poliomyelitis, similar memory responses are frequently observed following challenge with IPV or OPV despite the absence of serum neutralizing antibodies, presumably because of historic exposure to circulating poliovirus [20, 21].

The extent of poliovirus neutralizing antibody decline following immunization with IPV has been shown to depend on the degree of the response to the primary immunization series. Administration of smaller quantities of antigen during primary intramuscular immunization is associated with both a lower initial titer of neutralizing antibody and reduced persistence of detectable antibody [22, 23]. Furthermore, the lower titer of neutralizing antibody in individuals immunized with fractional doses remains apparent even after a booster dose with higher antigen content [22]. However, there is no experience with the long-term persistence of immunity following intradermal administration of fractional doses of IPV. The GMT following immunization with 1–3 doses of fractional (1/5) dose intradermal IPV is generally lower than that following full-dose intramuscular IPV and so it might be expected that titers would drop below the threshold for detection earlier [9–11]. However, whether this translates into lower protection against paralytic poliomyelitis is unknown and will depend on the degree of protection offered by residual immune memory.

The duration of the primed state following a single dose of intramuscular or intradermal IPV is also unknown. Anamnestic responses following a booster dose have been observed in studies up to 12 months after an initial single dose of IPV [15, 24]. Indeed, the extent of the antibody rise after boosting appears to increase with an increasing interval between the priming and booster dose up to about 6 months [24]. However, whether the primed state following a single dose of IPV persists beyond 12 months in the absence of immune boosting is unknown.

PROTECTION AGAINST POLIOMYELITIS

The development of serum neutralizing antibodies detectable at a dilution of 1 in 8 or higher is typically taken as a marker of

protective immunity against poliomyelitis following vaccination with IPV [6]. Immunological memory developed after a primary immunization series of 3–5 doses of IPV is also likely to be protective even in the absence of detectable neutralizing antibody in serum. The epidemiological observation of an absence of poliomyelitis in countries with long-term routine use of IPV supports this belief. Nonetheless, in some countries an adult booster with IPV is recommended for travelers to regions with continued poliovirus circulation.

It is less clear whether immunological priming after a single dose of IPV is protective against paralytic disease. Jonas Salk, the developer of IPV, believed that immunological memory following a single dose of IPV was protective against paralysis [5]. Analyzing poliovirus serology data from paralyzed and healthy children before the introduction of vaccines, he noted that children with antibodies only to serotype 2 appeared to be less likely to become paralyzed by serotype 1 compared with naive children [25]. He argued that this apparent heterotypic protection was analogous to homotypic priming by a single dose of IPV in the absence of homotypic antibody. However, there are limited data to support this argument, and Salk accepted that 2 doses of vaccine would be prudent when the first dose needs to be given before 6 months of age [5].

In Hungary, campaigns with monovalent OPVs as a method of poliomyelitis prevention were replaced in 1992 by routine immunization with a single dose of enhanced-potency IPV given at 3 months of age followed by 5 doses of trivalent OPV [26, 27]. In 2006 this sequential schedule was replaced with one based on IPV alone. No cases of VAPP were reported during 1992–2006, compared with 54 cases between 1961 and 1990 when only monovalent OPVs were in use [27]. This suggests that a single dose of IPV provides some protection against poliomyelitis. However, challenge with attenuated poliovirus, albeit at a high titer, is clearly different from exposure to the highly adapted wild-type poliovirus.

There are limited epidemiological data on the protective efficacy of a single dose of enhanced potency IPV. In Senegal, a case-control analysis during an outbreak of poliomyelitis in 1986–1987 resulted in an estimated efficacy of 36% after a single dose, although with very broad 95% confidence intervals (CIs) of 0%–67% [28]. The efficacy of 2 doses in this same study was 89% (95% CI, 62%–97%). In a pilot study of enhanced potency IPV in the North Arcot district of southern India, the protective efficacy of a single dose was estimated at 52% (95% CI, 10%–75%) and of 2 doses at 67% (95% CI, 37%–83%) using a case-control method applied to 210 cases reported during 1989–1992 (V. Balraj, R. Samuel, T. J. John, A. Hall, personal communication [3 June 2013]). The effectiveness of a single dose of first-generation IPV was inferred by Salk from the distribution of the number of individuals with poliomyelitis reported to have received 0 or 1 doses during 1959 in the United States [23]. Although this case-control analysis did not attempt to control for any confounders,

the protective efficacy of a single dose was 44% and of 2 doses was 82%, similar to that observed in Senegal and India. These estimates are also quite similar to the observed proportion of children seroconverting after a single dose of IPV (Figure 1). However, they should be interpreted with some caution—it is difficult to control for differences in exposure between cases and controls, particularly where multiple serotypes may be circulating, and this can lead to underestimation of the degree of protection offered by vaccination. Nonetheless, it is clear that a single dose of IPV is less effective than 2 doses against poliomyelitis.

There are no comparable studies with fractional-dose intradermal IPV because this vaccine has not been used in large-scale immunization studies.

DISCUSSION

A single, full dose of IPV administered intramuscularly at 3–4 months of age (corresponding to the second or third diphtheria-pertussis-tetanus [DPT] visit in many countries) will seroconvert approximately 50% of recipients. The limited data available suggest the protective efficacy of this vaccine against poliomyelitis would also be about 50%. The majority of recipients would also be immunologically primed (probably at least 90%), and they would therefore respond rapidly to a subsequent dose of vaccine. Earlier administration of vaccine results in poorer seroconversion as a result of interference by maternal antibodies [10, 11]. Coverage with the third dose of DPT is somewhat lower than with the first dose, and this may be marked in countries with poor overall routine immunization coverage. Furthermore, vaccination is typically delayed—by a median of 2 and 6 weeks for the first and third dose of DPT, respectively, in low- and middle-income countries [29, 30]. Therefore, if possible, administration of IPV should occur at the most appropriately timed visit, rather than be linked to delivery of a specific dose of DPT. Seroconversion may be higher among children receiving the vaccine at older ages, but no studies examined seroconversion after 1 dose beyond 4 months of age. If VAPP prevention while bivalent OPV continues to be used was of concern, then IPV could be given earlier [31].

Seroconversion is more limited after a single fractional (1/5) dose of IPV administered intradermally, with approximately 10%–40% expected to seroconvert when this vaccine is given at 3–4 months of age. There is no experience with the clinical efficacy of a single fractional-dose IPV, although it is also likely to be lower than for full-dose product.

Two full doses of IPV will seroconvert at least 80% of children when the first dose is administered at 10 weeks of age or later. A similar proportion of children will be protected against poliomyelitis based on available efficacy data. Seroconversion is better if the 2 doses are administered >4 weeks apart, although in the one identified study in which the first dose was given at approximately 10 weeks and the second 4 weeks later,

seroconversion occurred in 94%, 88%, and 100% of 17 infants [32]. These data therefore suggest that full-dose IPV given at the second and third DPT visit would be sufficiently immunogenic to protect at least 80% of recipients from poliomyelitis, although immunogenicity will be better where DPT is given later than the 6-, 10-, and 14-week schedule implemented in many countries (this is also apparent after 3 doses of IPV [33]). Alternatively, the first IPV dose could be given at the third DPT visit and the second with measles vaccine at 9 months or thereabouts. This may be favorable because the duration of protection offered by 2 doses of IPV has not been established, although it is known that persistence of detectable serum neutralizing antibodies to poliovirus is dependent on the strength of response to the initial immunization series [22, 23]. A longer interval between the first and second dose would result in higher antibody titers and therefore potentially a more durable response [24]. However, studies to formally establish the immunogenicity of this schedule are required. The level of coverage achieved with a measles vaccine given at 9 months should also be taken into account when considering this option.

Only one identified study examined the immunogenicity of 2 fractional (1/5) doses of enhanced potency intradermal IPV when the first dose was given after 10 weeks of age. This study showed seroconversion in 94%, 98%, and 93% of infants receiving fractional-dose intradermal IPV administered with a needle-free device at 4 and 8 months for serotypes 1, 2, and 3, respectively, compared with 100%, 100%, and 99% of infants receiving the full-dose product intramuscularly [9]. In general, the seroconversion data suggest that comparable protection against poliomyelitis would be offered by 2 doses of fractional-dose intradermal IPV compared with that achieved with full-dose product (approximately 80%; Figure 2). A note of caution is required, however, as neutralizing antibody GMT was consistently lower after fractional-dose product and the clinical efficacy of this vaccine has not been evaluated.

There are a number of limitations with the studies of seroconversion included in the systematic review. First, in the presence of maternal antibodies, seroconversion in the infant must be defined with reference to the expected antibody titer at the time of sample collection in the absence of vaccination. This is typically inferred from the titer measured at baseline and a half-life of approximately 28–30 days. It is possible that this method will over- or underestimate seroconversion if the decline in antibody titer deviates from this pattern. Second, children may seroconvert as a result of exposure to wild poliovirus or secondary spread of vaccine poliovirus by children vaccinated with OPV. The former is relatively rare, although it was clearly apparent in one study included in the systematic review [8]. Secondary exposure to vaccine poliovirus could have occurred in all studies based on their date and location, with the exception of the 2 Cuban studies that were timed to occur between national immunization days with OPV [9, 11]. The proportion of children seroconverting in

these 2 studies was consistent with the results from the other studies after adjusting for the age at administration (Supplementary Tables 1 and 2). Finally, study staff could not be blinded to the vaccine administered when fractional intradermal and full-dose intramuscular IPV were compared. However, laboratory testing was blind to the vaccine administered in at least 3 of the 4 studies, minimizing the risk of any potential bias.

IPV clearly induces herd immunity sufficient to eliminate poliovirus transmission in high-income countries [34]. However, there is very limited experience of the impact of this vaccine on poliovirus transmission in middle- and low-income countries. Mucosal immunity induced by IPV against poliovirus shedding in stool is significantly reduced compared with OPV [35]. The impact of this vaccine in countries where poliovirus transmission is more efficient could also be limited, particularly if the fecal-oral route is important. Vaccination coverage achieved by routine immunization programs in these settings should also be considered when estimating the likely impact of IPV on transmission of any reintroduced or reemerged poliovirus. A recent mathematical modeling study suggested that routine immunization with IPV would be beneficial under most outbreak scenarios, although rarely it could allow “silent” transmission by preventing poliomyelitis but not poliovirus shedding [36]. There was considerable uncertainty about the degree of benefit, given limited data on the impact of IPV on poliovirus transmission in different settings.

Irrespective of the degree of herd immunity provided by IPV, it can clearly mitigate the health impact of any reintroduced or reemerged poliovirus after the global withdrawal of OPV serotypes, by protecting individuals from paralytic disease. A single full dose of IPV given at 3–4 months of age is likely to protect about half of recipients, while 2 full doses administered after 10 weeks of age would protect at least 80%. Therefore, in countries at risk of poliovirus outbreaks, 2 doses are likely to be preferred over a single dose. Fractional dosing may make this option more affordable, and seroconversion after 2 doses was comparable with the full-dose product (but not after 1 dose). However, there is no programmatic experience with this vaccine, and its effectiveness will depend on the feasibility of intradermal administration with needles or needle-free devices and the associated costs.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (<http://jid.oxfordjournals.org/>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. I would like to thank Vinohar Balraj, T. Jacob John, Reuben Samuel, and Andrew Hall for sharing unpublished data, and Roland Sutter, Elizabeth Miller, and Bruce Aylward for helpful discussion.

Financial support. This work was supported by grants from the Royal Society and the UK Medical Research Council. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Supplement sponsorship. This article is part of a supplement entitled “The Final Phase of Polio Eradication and Endgame Strategies for the Post-Eradication Era,” which was sponsored by the Centers for Disease Control and Prevention.

Potential conflicts of interest. The author is a member of the World Health Organization SAGE working group on polio.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Global Polio Eradication Initiative. Polio eradication and endgame strategic plan 2013–2018. <http://bit.ly/1649OwE>. Accessed 10 July 2013.
2. World Health Organization. Conclusions and recommendations of the Ad Hoc Advisory Committee on Poliomyelitis Eradication, Geneva, 21–22 September 2004. *Wkly Epidemiol Rec* **2004**; 79:401–8.
3. World Health Organization. Meeting of the Strategic Advisory Group of Experts on immunization, November 2012—conclusions and recommendations. *Wkly Epidemiol Rec* **2013**; 88:1–16.
4. Oliver Wyman Inc. Global post-eradication IPV supply and demand assessment: integrated findings. Commissioned by the Bill & Melinda Gates Foundation, 2009. <http://www.polioeradication.org/Research/PolioPipeline/No4Summer2009/GlobalposteradicationIPV.aspx>. Accessed 2 June 2013.
5. Salk J. One-dose immunization against paralytic poliomyelitis using a noninfectious vaccine. *Rev Infect Dis* **1984**; 6:S444–50.
6. Plotkin AA, Vidor E. Poliovirus vaccine—inactivated. In: Plotkin SA, Orenstein WA, eds. *Vaccines*. 4th ed. Philadelphia: Saunders, 2004: 625–49.
7. Vidor E, Meschievitz C, Plotkin S. Fifteen years of experience with Vero-produced enhanced potency inactivated poliovirus vaccine. *Pediatr Infect Dis J* **1997**; 16:312–22.
8. Jain PK, Dutta AK, Nangia S, Khare S, Saili A. Seroconversion following killed polio vaccine in neonates. *Indian J Pediatr* **1997**; 64:511–5.
9. Resik S, Tejada A, Sutter RW, et al. Priming after a fractional dose of inactivated poliovirus vaccine. *New Engl J Med* **2013**; 368:416–24.
10. Mohammed AJ, AlAwaidey S, Bawikar S, et al. Fractional doses of inactivated poliovirus vaccine in Oman. *N Engl J Med* **2010**; 362: 2351–9.
11. Resik S, Tejada A, Lago PM, et al. Randomized controlled clinical trial of fractional doses of inactivated poliovirus vaccine administered intradermally by needle-free device in Cuba. *J Infect Dis* **2010**; 201: 1344–52.
12. Wahid R, Cannon MJ, Chow M. Virus-specific CD4+ and CD8+ cytotoxic T-cell responses and long-term T-cell memory in individuals vaccinated against polio. *J Virol* **2005**; 79:5988–95.
13. Hammon WM, Coriell LL, Ludwig EH, et al. Evaluation of Red Cross gamma globulin as a prophylactic agent for poliomyelitis. 5. Reanalysis of results based on laboratory-confirmed cases. *J Am Med Assoc* **1954**; 156:21–7.
14. Salk D, Vanwezel AL, Salk J. Induction of long-term immunity to paralytic poliomyelitis by use of non-infectious vaccine. *Lancet* **1984**; 2: 1317–21.
15. Swartz TA, Handsher R, Stoeckel P, et al. Immunologic memory induced at birth by immunization with inactivated polio vaccine in a reduced schedule. *Eur J Epidemiol* **1989**; 5:143–5.
16. Salk J, Stoeckel P, Vanwezel AL, Lapinleimu K, Vansteenis G. Antigen content of inactivated poliovirus vaccine for use in a one-dose or 2-dose regimen. *Ann Clin Res* **1982**; 14:204–12.
17. Bottiger M. Polio immunity to killed vaccine—an 18-year follow-up. *Vaccine* **1990**; 8:443–5.

18. Faden H, Duffy L, Sun M, Shuff C. Long-term immunity to poliovirus in children immunized with live attenuated and enhanced-potency inactivated trivalent poliovirus vaccines. *J Infect Dis* **1993**; 168:452–4.
19. Bottiger M. Antibody stimulation in individuals without demonstrable poliovirus antibodies following a fifth injection of inactivated poliovirus vaccine. *Acta Path Micro Im B* **1973**; B81:795–8.
20. Rumke HC, Oostvogel PM, Vansteenis G, Vanloon AM. Poliomyelitis in the Netherlands—a review of population immunity and exposure between the epidemics in 1978 and 1992. *Epidemiol Infect* **1995**; 115:289–98.
21. Abbink F, Buisman AM, Doornbos G, Woldman J, Kimman TG, Conyn-van Spaendonck MA. Poliovirus-specific memory immunity in seronegative elderly people does not protect against virus excretion. *J Infect Dis* **2005**; 191:990–9.
22. Salk JE. How many injections of poliomyelitis vaccine for effective and durable immunity. *J Am Med Assoc* **1958**; 167:1–7.
23. Salk JE. Persistence of immunity after administration of formalin-treated poliovirus vaccine. *Lancet* **1960**; 2:715–23.
24. Salk J. Future prospects for vaccination against virus diseases. *Behring Institute Mitteilungen* **1982**; 71:34–42.
25. Salk JE. Requirements for persistent immunity to poliomyelitis. *Trans Assoc Am Physicians* **1956**; 69:105–14.
26. Estivariz CF, Molnar Z, Venczel L, et al. Paralytic poliomyelitis associated with Sabin monovalent and bivalent oral polio vaccines in Hungary. *Am J Epidemiol* **2011**; 174:316–25.
27. Kapusinszky B, Molnar Z, Szomor KN, Berencsi G. Molecular characterization of poliovirus isolates from children who contracted vaccine-associated paralytic poliomyelitis (VAPP) following administration of monovalent type 3 oral poliovirus vaccine in the 1960s in Hungary. *FEMS Immunol Med Microbiol* **2010**; 58:211–7.
28. Robertson SE, Drucker JA, Fabreteste B, et al. Clinical efficacy of a new, enhanced-potency, inactivated poliovirus vaccine. *Lancet* **1988**; 331:897–9.
29. Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. *Lancet* **2009**; 373:1543–9.
30. Akmatov MK, Mikolajczyk RT. Timeliness of childhood vaccinations in 31 low and middle-income countries. *J Epidemiol Community Health* **2012**; 66:e14.
31. Miller MA, Sutter RW, Strebel PM, Hadler SC. Cost-effectiveness of incorporating inactivated poliovirus vaccine into the routine childhood immunization schedule. *J Am Med Assoc* **1996**; 276:967–71.
32. Simoes EA, Padmini B, Steinhoff MC, Jadhav M, John TJ. Antibody-response of infants to 2 doses of inactivated poliovirus vaccine of enhanced potency. *Am J Dis Child* **1985**; 139:977–80.
33. Dayan GH, Thorley M, Yamamura Y, et al. Serologic response to inactivated poliovirus vaccine: a randomized clinical trial comparing 2 vaccination schedules in Puerto Rico. *J Infect Dis* **2007**; 195:12–20.
34. Murdin AD, Barreto L, Plotkin S. Inactivated poliovirus vaccine: past and present experience. *Vaccine* **1996**; 14:735–46.
35. Hird TR, Grassly NC. Systematic review of mucosal immunity induced by oral and inactivated poliovirus vaccines against virus shedding following oral poliovirus challenge. *PLoS Pathog* **2012**; 8:e1002599.
36. Mangal TD, Aylward RB, Grassly NC. The potential impact of routine immunization with inactivated poliovirus vaccine on wild-type or vaccine-derived poliovirus outbreaks in a posteradication setting. *Am J Epidemiol* **2013**; 178:1579–87.

Background Paper on Whole-Cell, Killed, Oral Cholera Vaccines

Prepared by the SAGE Working Group on Oral Cholera Vaccines, the World Health Organization (WHO) Secretariat, and the Centers for Disease Control and Prevention

March 31, 2017

Table of Contents

Section No.	Content	Page No.
1.	Executive Summary	3
1.1.	Preamble	3
1.2.	Key Data and Conclusions	4
1.3.	Proposed Key Recommendations	5
2.	Introduction and Background	8
2.1.	Key Points	8
2.2.	Introduction	9
2.3.	Previous Recommendations from the 2010 Position Paper	11
2.4.	Global Taskforce on Cholera Control	12
2.5.	Magnitude of the Problem of Cholera	14
2.6.	Cholera Surveillance – Epidemiology and Laboratory	18
2.7.	Cholera Treatment	20
2.8.	Cholera Prevention	20
3.	Currently Available, Whole Cell, Killed Oral Cholera Vaccines	21
3.1.	Key Points	21
3.2.	Details of the available Whole-Cell, Killed Oral Cholera Vaccines	21
3.3.	Review of Scientific Evidence	32
3.4.	Global Oral Cholera Vaccine Stockpile	57
4.	Grading for Recommendations, Assessment, Development and Evaluation (GRADE)	60
4.1.	Introduction and Selected Questions for Review	60
4.2.	Methodology	60
4.3.	Results	61
5.	Proposed Recommendations for SAGE Consideration	62
5.1.	General Recommendations	62
5.2.	Recommendations for Control of Endemic Cholera	63
5.3.	Recommendations for Cholera Control in Humanitarian Emergencies	64
5.4.	Recommendations for Control of Cholera Outbreaks	64
5.5.	Additional Research and Evaluation Recommendations	64
6.	Other Cholera Vaccines in Development	66
7.	References	69
8.	Appendices	76
8.1.	Appendix 1: SAGE Working Group on Oral Cholera Vaccines	76
8.2.	Appendix 2: SAGE Evidence to Recommendations Table	78
8.3.	Appendix 3: Evidence Review GRADE Tables	84
8.4.	Appendix 4: Final GRADE Tables and Conclusions	118
8.5.	Appendix 5: Submitted Manuscript (Protection from OCVs – Meta-analysis and systematic review)	122

1. Executive Summary

1.1. Preamble

Cholera, an acute watery diarrheal disease, caused by toxigenic strains of the bacterium *Vibrio cholerae* O1 and O139, causes an estimated over 2.9 million cases and over 95,000 deaths annually in cholera endemic countries alone and frequent epidemics in other settings with poor water and sanitation infrastructure. Global estimates range from 1.4 – 4.8 million cases and 28,000 – 142,000 deaths every year. The disease is characterized by acute onset watery diarrhea leading to rapid dehydration and death, if not promptly treated with fluid replacement and antibiotics for severe cases. Cholera is transmitted through the fecal-oral route most frequently by way of contaminated water and food and, hence, primarily occurs in settings of poor water and sanitation infrastructure in sub-Saharan Africa, Asia, and more recently in Haiti. Additional complex humanitarian emergencies in recent times, with resulting infrastructure disruptions and population displacements, have added a significant cholera burden globally.

Provision of safe water, adequate sanitation, improved hygiene measures (WaSH), cholera treatment, and cholera vaccination form a toolkit of interventions for comprehensive cholera prevention and control. Cholera vaccination is an important short- to medium-term tool for cholera prevention and control while longer-term interventions for water and sanitation infrastructure systems are put into place and in crisis/refugee settings where longer term infrastructure changes are not feasible. Three killed, whole-cell (WC) oral cholera vaccines (OCVs) are currently prequalified by the World Health Organization (WHO) for procurement by United Nations agencies and are available for global use: Dukoral, Shanchol and Euvichol (Shanchol and Euvichol are available through the global OCV stockpile). In 2010, the WHO issued a revised position statement based on data available at the time with the recommendations that OCVs should be considered in preemptive situations (prevention before an outbreak starts) as part of comprehensive cholera control plans, and could be considered in reactive situations (once an outbreak starts) depending on the local epidemiology and feasibility of conducting campaigns. The recommendations emphasized the need to sustain critical cholera control interventions in outbreak situations and additional documentation of these experiences given very limited OCV use in outbreak settings. Since 2010, there has been tremendous progress on global availability of vaccines and numerous OCV use experiences in both clinical trial and programmatic settings. In June 2013, a global OCV stockpile with an initial stock of 2 million doses was established by WHO with funding support from multiple donors, and in November 2013, Gavi (the Vaccine Alliance) endorsed funding support for the OCV stockpile. The Global Taskforce for Cholera Control (GTFCC) was revitalized by WHO, serving as the secretariat with representation of key global, regional and country partners.

During 2010 – 2016, cholera has continued to be a significant problem globally with large scale epidemics, such as the one experienced in Haiti, and surges in endemic settings of sub-Saharan Africa and Asia leading to increasing efforts by partners to utilize all available tools, including vaccines as part of comprehensive cholera prevention and control programs. This global problem combined with multiple OCV use experiences provide additional data and lessons learned to review and update recommendations for oral cholera vaccine use by the WHO Strategic Advisory Group of Experts on Immunization (SAGE). In November 2015, the WHO SAGE working group on oral cholera vaccines (**Appendix 1**) was established to review the progress made since the last OCV position paper update of 2010.

This background document presents updated information on whole-cell, killed, oral cholera vaccines since the previous oral cholera vaccine position paper (2010), describes the relevant data reviewed by the working group and the resulting proposed recommendations for whole-cell, killed oral cholera vaccines for SAGE deliberation and consideration.

1.2. Key Data and Conclusions

- Several large-scale epidemics, surges in endemic cholera, and multiple humanitarian emergencies have occurred within the last few decades, including since 2010. Cholera continues to cause significant morbidity and mortality globally.
- Oral cholera vaccines (OCVs) prequalified by WHO are available for global use in endemic, epidemic/outbreak and humanitarian emergency situations.
- An OCV stockpile, supported by Gavi and managed by the International Coordinating Group (ICG) is available for rapid access to OCVs in outbreak and humanitarian emergency situations. An additional ‘non-emergency reserve’ of stockpile vaccine, also supported by Gavi and managed by the OCV working group of the GTFCC, is available for endemic situations. Since the establishment of the stockpile, over 7 million doses from the stockpile have been deployed in over 14 countries in multiple endemic, epidemic, and emergency situations.
- Key conclusions of the evidence review by the SAGE OCV working group, including the Grading for Recommendations, Assessment, Development and Evaluation (GRADE) review for vaccine safety, efficacy (and effectiveness) and safety among pregnant women, are:
 - Vaccine Safety: there is high level of scientific evidence that the currently available WC, killed OCVs are safe among non-pregnant individuals ≥ 1 year old.
 - Vaccine Efficacy and Effectiveness: there is moderate level of scientific evidence that the currently available WC killed OCVs are efficacious and effective with a duration of at least 6 months for a single dose. There is moderate level of scientific evidence that the currently available whole-cell killed oral cholera vaccines with a 2-dose schedule are efficacious and effective for at least 3 years among adults, but not among young children 1 – 5 years old. There is low level of scientific evidence that the currently available WC killed OCVs are effective for at least 5 years (only 2 studies).
 - Vaccine Safety among Pregnant Women: there is moderate level of scientific evidence that the currently available WC killed OCVs are safe for use among pregnant women.
 - Feasibility and Acceptability: OCVs campaigns have been demonstrated to be feasible and acceptable in multiple endemic, epidemic and humanitarian emergency settings.
 - Cost-effectiveness: data on cost-effectiveness is limited and most studies and evaluations have reported costing data only. Modeling studies suggest that cholera vaccination has the potential to be a cost-effective intervention for cholera control in countries at high risk for cholera.

1.3. Proposed Key Recommendations for SAGE Consideration

General Recommendations

1. Given the current availability of prequalified WC killed oral cholera vaccines (OCVs) and data on their safety, efficacy, field effectiveness, feasibility, impact and acceptability in cholera-affected populations, these vaccines should be used in areas with endemic cholera, in humanitarian crisis with high risk of cholera and during cholera outbreaks, in conjunction with other cholera prevention and control strategies.
2. Appropriate case management, WaSH interventions, surveillance and community mobilization remain cornerstones of cholera control. Vaccination is synergistic with those activities.
3. The main objective of vaccination is to reduce disease burden in vaccinated areas, through individual and herd protection, and to prevent the spatial expansion of outbreaks.
4. Mass vaccination campaigns are usually the most practical option for delivering oral cholera vaccines. Schools, religious institutions and other community settings can be appropriate venues for vaccination campaigns using fixed sites. Outreach activities can also be organized. Incorporating cholera vaccination with other vaccination activities can be an alternative or complementary strategy to mass campaigns.
5. Cholera vaccination mass campaigns should be accompanied by WaSH interventions and combined with other health-related interventions.
6. Epidemiological and laboratory surveillance is essential to estimate the burden of disease and understand the impact of vaccination and other interventions.
7. Equitable access to OCV should be ensured for underserved populations exposed to the risk of cholera. OCV stockpiles, supported by GAVI and managed by the ICG (for emergency type of use) and by the GTFCC OCV working group (for use in endemic settings), have been formally established in 2013 for that purpose. Requests to access OCV in any setting should follow the established mechanisms of stockpile management.
8. In all settings, a series of criteria should be considered to guide the decision to vaccinate,
 - The risk of cholera among targeted populations
 - The susceptibility and vulnerability of the population and the risk of spatial extension.
 - The capacity to cover as many persons as possible, eligible to receive the vaccine and living in the targeted area (e.g., ages ≥ 1 or 2 years, depending on the vaccine).
 - Programmatic factors such as the local capacity to organize and conduct a campaign, ability to provide other priority health interventions and population acceptability.

- Cholera vaccination should not be conducted if a campaign has been conducted in the previous 3 years in the same population (with consideration for the quality of the campaign, the vaccine coverage, and any population movements)
9. Countries and agencies accessing the OCV stockpiles should systematically implement M&E activities and provide accompanying data to WHO GTFCC. In particular, M&E activities should provide better estimates of,
 - The impact of OCV to control and prevent cholera outbreaks, including in humanitarian emergency situations
 - The impact of OCV on cholera transmission in endemic settings
 - The vaccine effectiveness using different vaccination strategies and in different age groups
 - The cost-effectiveness of different vaccination strategies and in various settings and age groups
 Guidelines have been developed for this purpose and are accessible on the WHO website.
 10. Based on available evidence, there are considerable benefits and very few risks for including pregnant women in OCV vaccination campaigns.
 11. OCV should be considered for emergency/relief workers who are likely to be directly exposed to cholera patients or to contaminated food or water, particularly those staying in areas with poor access to healthcare facilities.
 12. Vaccination is generally not recommended for long- or short-term travelers to cholera-affected countries.

Control of Endemic Cholera

1. Cholera vaccination should be targeted in priority to high-risk areas or groups, regularly affected by cholera; with culture-confirmed cases detected in at least three out of the last five years and evidence of local transmission. Campaign planning should be carried out to ensure that vaccination takes place prior to any known cholera season.
2. Cholera vaccination in endemic areas should be contingent on multisectoral interventions as part of a long-term plan for cholera prevention and control endorsed at the local and national levels by the relevant ministries and should be budgeted for.
3. Universal vaccination (throughout a country without regard to risk) is not recommended in most countries.
4. Follow up campaigns in the same areas may be considered after 3 years in case of persistent transmission.
5. Strategies targeting specific age groups at higher risk may be considered.

Cholera Control in Humanitarian Emergencies

1. During humanitarian emergencies with a risk of cholera, but without a current cholera outbreak, vaccination with OCV should systematically be considered to help prevent potential outbreaks, as an additional preparedness measure, depending on the local infrastructure (i.e., capacity to organize a vaccination campaign).
2. The decision to vaccinate should be guided by a thorough investigation of the current and historical epidemiological situation, an assessment of the actual risk of cholera, and a clear identification of geographical areas and populations to be targeted.
3. Campaign planning should be carried out to ensure that vaccination takes place prior to any known cholera season. Campaign preparation should be conducted early to ensure that vaccination starts immediately once the vaccines become available in country.
4. In areas of protracted emergencies, follow-up campaigns may be considered after 3 years (or less in case of persistent risk, particularly in case of population movement).

Control of Cholera Outbreaks

1. Cholera vaccination should systematically be considered to help prevent the spread of current outbreaks to new areas, following a thorough investigation of the current and historical epidemiological situation and a clear identification of geographical areas and populations to be targeted.
2. Campaign preparation should be conducted early to ensure that vaccination starts immediately once the vaccines become available in country.
3. Based on available evidence on short-term protection, a single dose strategy could be considered in areas experiencing cholera outbreaks. Considering the limited evidence about the duration of protection, additional vaccination might be needed to ensure longer-term protection.

Additional research and evaluation recommendations are available in Section 5.

2. Introduction and Background

2.1. Key points

1. In 2010, the World Health Organization (WHO) recommended the preemptive use of the available WC killed OCVs in endemic areas among high-risk populations and in areas at risk areas of outbreaks in conjunction with traditional cholera prevention and control interventions. The WHO also recommended that reactive use of OCVs should be considered in active outbreak situations depending on a thorough assessment of the local epidemiological factors, infrastructure and capacity.
2. In May 2011, the World Health Assembly adopted a resolution calling for the implementation of an integrated and comprehensive approach to cholera control, including the use of oral cholera vaccines, where appropriate, in conjunction with other recommended prevention and control methods.
3. Large, protracted cholera outbreaks continue to occur in many parts of the world, including sub-Saharan Africa, and Asia, and in Haiti, which has experienced the largest, most protracted cholera epidemic of modern times.
4. Two newer WC killed OCVs have been prequalified by WHO (Shanchol in 2011 and Euvichol in 2015). Several million doses of Shanchol have been used for cholera prevention and response thus far. New data have become available regarding the safety, acceptability, effectiveness, impact and cost-effectiveness of the vaccines, and their role in a comprehensive, integrated cholera prevention and control strategy.
5. Uncertainties regarding OCV supply and demand predictions prompted the creation of a global OCV stockpile. In 2013, the global OCV stockpile was created with an initial commitment of 2 million doses primarily for outbreak and humanitarian emergency response. In November 2013, Gavi, the Vaccine Alliance approved investment support of US\$115 million for the global OCV stockpile during 2014 – 2018, and in June 2016, the Gavi board endorsed support for operational costs of OCV campaigns. Since 2013, over 7 million OCV doses have been deployed from the global stockpile in over 14 countries and vaccine availability is expected to increase with a second prequalified vaccine.
6. In 2014, the Global Taskforce for Cholera Control (GTFCC), was revitalized and an OCV working group was established to provide guidance and recommendations for OCV use in different settings and inform further guidance.
7. These new developments and availability of additional data make this an opportune time for WHO SAGE to revisit and update its recommendations for the use of WC killed OCVs.

2.2. Introduction

Cholera is an acute diarrheal infection caused by ingestion of toxigenic serogroups O1 and O139 of the bacterium *Vibrio cholerae* through direct fecal-oral contamination or ingestion of contaminated water or food. Rapid dehydration and death can occur in a matter of hours, if not promptly and adequately treated with fluid replacement. Cholera primarily occurs in areas with poor access to safe drinking water and inadequate sanitation infrastructure. It remains an important, preventable but neglected public health problem, affecting the most impoverished populations, including those displaced as a result of humanitarian emergencies. It imposes substantial costs on families and public health systems.

Cholera causes an estimated 1.4 to 4.3 million cases, and 28,000 to 142,000 deaths per year worldwide¹. Over 1.4 billion persons are at risk globally¹ and large scale, protracted epidemics are increasing in frequency compounded by growing occurrence of complex emergencies that result in the breakdown of infrastructure or population displacements. While epidemic cholera attracts attention and accounts for most of the cases reported to WHO each year, endemic cholera continues to exact an unacceptable toll primarily in large parts of Africa, South and Southeast Asia, and more recently in the Americas (Haiti). In 2015, a total of 172,454 cases and 1,304 deaths were reported to the World Health Organization (WHO) by 42 countries with an overall case-fatality rate (CFR) of 0.8%². This, however, only represents a fraction of cases due to lack of diagnostic facilities and massive underreporting. The disease is largely underreported due to several factors and many countries and regions report cases as “acute watery diarrhea” and not cholera. Underreporting may be due to factors such as inadequate disease surveillance and reporting, fear of the macro-economic impact of cholera reports on trade and tourism, and poor access to health services among the very poor and marginalized populations, who are at the highest risk of morbidity and mortality.

The provision of safe drinking water, adequate sanitation, hygiene promotion and robust disease surveillance remain the mainstays of preventing both endemic and epidemic cholera. Fluid replacement, with oral rehydration solution (ORS) if the patient can tolerate intake by mouth, or IV fluids followed by ORS for severe dehydration, serves as the primary treatment for cholera (<http://www.who.int/cholera/en/>). Additionally, antimicrobial therapy, as an adjunct to fluid resuscitation, has been shown to decrease the duration and volume of diarrhea in cholera patients with severe dehydration^{3,4}. Providing populations with widespread access to safe drinking water and effective sanitation are the most durable means of preventing cholera and other enteric diseases, and have additional public health benefits. However, large infrastructure improvements require long term financing, sustained maintenance, and require financial resources that have been demonstrated in practice to be beyond the reach of most of the populations at high risk in the near future, and are sometimes impossible (for example in acute emergencies and displaced populations). Short- to medium term interventions to prevent and control cholera are needed to bridge the gap while long term water, sanitation and hygiene infrastructure is created and maintained. Cholera vaccination is a key option for cholera prevention and control, and appropriate and targeted use of cholera vaccines is increasingly being recognized as a useful complement to improving water, sanitation, and hygiene measures within a comprehensive cholera control strategy⁵. In 2011, the 64th World Health Assembly passed a resolution to consider integrated cholera control strategies, including vaccination, in endemic and epidemic situations (https://www.stopcholera.org/sites/cholera/files/resolution_cholera_a64_r15-en.pdf).

Oral cholera vaccines (OCVs) have been available since the 1990s⁵. A two-dose vaccine consisting of killed whole cells of *V. cholerae* O1 (including classical and El Tor biotypes and Inaba and Ogawa serotypes) and the B subunit of the cholera toxin (WC-rBS), was produced by SBL Vaccin (now by Crucell) and sold as

Dukoral, was prequalified in 1991. Although several field studies with Dukoral were conducted and yielded encouraging results, its use has largely been limited to individual use for travelers from non-endemic to endemic countries. Following a series of technology transfers, a modified whole-cell killed bivalent (O1 and O139) vaccine without the B subunit, was manufactured in Vietnam (ORCVAX/mORCVAX – for local use in Vietnam) and later, India (marketed as Shanchol) and Republic of Korea (Euvichol). Both Shanchol and Euvichol have been prequalified by WHO since September 2011 and December 2015 respectively. Other vaccine candidates are also in different early and late stages of development and are included in the section on ‘other oral cholera vaccines’.

In March 2010, WHO issued a position statement regarding OCV use⁵. WHO recommended targeted use of OCVs in endemic settings, in conjunction with other prevention and control strategies. In outbreak situations and during complex emergencies, WHO stated that preemptive vaccination ‘should’ be considered in areas determined to be at imminent risk for infection, after taking into account the local epidemiologic context and capacity to mount a vaccination campaign, and that reactive vaccination once an outbreak had started ‘could’ be considered based on the local epidemiological features and response capacity. Given limited reactive vaccine use at the time, WHO encouraged countries and regions to document such experiences.

Several new developments have occurred since the last WHO position paper in 2010, 1) large-scale, protracted outbreaks have continued to occur worldwide. Cholera appeared in Haiti in 2010, and has resulted in the largest protracted epidemic in recent times; endemic areas of sub-Saharan Africa, and Asia have experienced large scale increases in cases and deaths, 2) in addition to Dukoral, which was prequalified in 1991, two easier-to-use OCVs (Shanchol and Euvichol) were prequalified by WHO. Several million doses of Shanchol (and mORCVAX in Vietnam) have been used in public health settings resulting in more available data on safety, efficacy, duration of protection, field effectiveness, impact and cost-effectiveness, 3) the global OCV stockpile was established to ensure that supply would be available for prompt response in outbreak and emergency settings⁶, and Gavi endorsed funding support for the stockpile by committing US\$115 million over 5 years from 2014–2018 (<http://www.gavi.org/support/nvs/cholera-vaccine/>), 4) the Global Taskforce for Cholera Control (GTFCC) was revitalized in 2014, and an OCV working group established under the GTFCC has been instrumental in reviewing evidence for OCV use in different settings, including an expansion of stockpile OCV use in endemic settings.

In November 2015, a SAGE OCV working group was established to review evidence regarding safety, effectiveness, acceptability, cost-effectiveness and impact on cholera transmission of OCVs since the 2010 WHO recommendations.

This document is intended to provide a detailed update on new developments and data regarding cholera and the currently available, whole-cell, killed oral cholera vaccines after 2010 to inform discussions and recommendations by the WHO SAGE during its meeting in April 2017.

2.3. Previous Recommendations from the 2010 WHO Position Paper on Oral Cholera Vaccines

- Cholera control should be a priority in areas where the disease is endemic. Given the availability of 2 oral cholera vaccines and data on their efficacy, field effectiveness, feasibility and acceptance in cholera-affected populations, immunization with these vaccines should be used in conjunction with other prevention and control strategies in areas where the disease is endemic and should be considered in areas at risk for outbreaks.
- Vaccination should not disrupt the provision of other high-priority health interventions to control or prevent cholera outbreaks. Vaccines provide a short-term effect that can be implemented to bring about an immediate response while the longer term interventions of improving water and sanitation, which involve large investments, are put into place.
- In cholera-endemic countries, vaccinating the entire population is not warranted. Rather, vaccination should be targeted at high-risk areas and population groups. The primary targets for cholera vaccination in many endemic areas are preschool-aged and school-aged children. Other groups that are especially vulnerable to severe disease and for which the vaccines are not contraindicated may also be targeted, such as pregnant women and HIV-infected individuals. Periodic mass vaccination campaigns are probably the most practical option for delivering cholera vaccines. Incorporating cholera vaccination into routine vaccination schedules may be an alternative or complementary strategy to mass vaccination campaigns.
- Since the documented duration of significant protection for the oral cholera vaccine is 2 years, it is recommended that initial vaccination with 2 doses be followed by a booster dose every second year. Once data on the longer-term efficacy of any oral cholera vaccine become available, the recommended interval between initial and booster vaccination may be extended.
- The mainstay of control measures to be implemented during ongoing epidemics should remain (i) providing appropriate treatment to people with cholera, (ii) implementing interventions to improve water and sanitation and (iii) mobilizing communities. Pre-emptive vaccination should be considered by local health authorities to help prevent potential outbreaks or the spread of current outbreaks to new areas. Finalizing of predictive risk-assessment tools to help countries determine when pre-emptive cholera vaccination might be used is needed urgently; these tools should be made available and field-tested as soon as possible.
- Given the recent large and prolonged outbreaks of cholera (for example, in Angola and Zimbabwe), reactive vaccination could be considered by local health authorities as an additional control measure, depending on the local infrastructure and following a thorough investigation of the current and historical epidemiological situation, and clear identification of geographical areas to be targeted. Considering the lack of experience with implementing reactive vaccination against cholera, the feasibility and impact of vaccination in halting ongoing outbreaks should be documented and widely disseminated. Pre-emptive or reactive vaccination should cover as many people as possible who are eligible to receive the vaccine (for example, children aged ≥ 1 years or ≥ 2 years, depending on the vaccine), and should be conducted as quickly as possible.
- It is strongly recommended that surveillance for microbiologically confirmed cases of cholera be instituted and integrated into already existing surveillance systems or networks to measure the burden of disease and monitor the seasonality and the impact of vaccination and other interventions in high-risk populations.

2.4. The Global Taskforce on Cholera Control (GTFCC)

The Global Task Force on Cholera Control (GTFCC) is a network of partner institutions which was revitalized in response to the 2011 World Health Assembly (WHA) resolution for “Cholera mechanisms for control and prevention”. The goal of the GTFCC was to strengthen WHO’s work on cholera prevention and control, including improved collaboration and coordination among relevant WHO departments and other relevant stakeholders. A revitalization process was initiated in December 2012 and completed in early 2014.

The objectives of the GTFCC are to, 1) support the design and implementation of global strategies to contribute to capacity development for cholera prevention and control globally, 2) provide a forum for technical exchange, coordination, and cooperation on cholera-related activities to strengthen countries’ capacity to prevent and control cholera, especially those related to implementation of proven effective strategies and monitoring of progress, dissemination and implementation of technical guidelines, operational manuals, etc., 3) support the development of a research agenda with special emphasis on evaluating innovative approaches to cholera prevention and control in affected countries, 4) increase the visibility of cholera as an important global public health problem through integration and dissemination of information about cholera prevention and control, and conducting advocacy and resource mobilization activities to support cholera prevention and control at national, regional, and global levels.

The first meeting of the GTFCC was conducted in June 2014, following which 7 working groups were established over the next 1 – 2 years, and included working groups on, a) epidemiology and surveillance, b) laboratory and surveillance, c) oral cholera vaccines, d) case management, e) water, sanitation and hygiene (WaSH), f) communications, advocacy and social mobilization, g) training. Of the 7 working groups envisaged, 5 are fully functional. The goal of the working groups has been to review evidence and provide guidance to the GTFCC in key domains of cholera prevention and control. Below are some key areas of work accomplished by the five working groups within their respective domains.

a) Epidemiology and Surveillance Working Group

- Development of standardized surveillance terms and updated case definitions, including coordination with the laboratory and surveillance working group on use of RDTs and molecular diagnostics for surveillance.
- Ongoing work on updating existing guidance (“Yellow Book”) on cholera outbreaks and response.

b) Laboratory and Surveillance Working Group

- Development of a guidance note on potential use of available rapid diagnostic tests (RDTs), including when and where to use RDTs, interpretation of results and test characteristics with limits and performance. Ongoing work to define target product profile for ideal RDTs and facilitation of RDT prequalification process.
- Development of a WHO briefing document with updated information on the use of DNA-based molecular techniques for field usage.
- Ongoing work to harmonize antimicrobial susceptibility testing for resistance detection and verification to avoid conflicting results.

- c) Oral cholera vaccines Working Group
- Development and review of a guidance note on OCV use in pregnancy, including a comprehensive review of existing literature.
 - Development and review of a guidance note on OCV use among international travelers, including a comprehensive review of existing literature.
 - Review and voting on OCV use requests in endemic hotspot situations (e.g., Haiti OCV use request)
 - Ongoing work on prioritization of the OCV research agenda and integration with other cholera control measures.
- d) Case Management/Patient Care Working Group
- Agreement on standardized approaches to organization of case management in outbreak situations, infection control practices at different levels of care and use of antibiotics for cholera treatment.
 - Validation of current recommendations on use of oral rehydration solution (ORS), intravenous fluids and zinc.
 - Validation of current recommendations on treatment of children with severe acute malnutrition and cholera.
 - Ongoing work with a review of the current knowledge on treatment of pregnant women with cholera.
- e) Water, Sanitation and Hygiene (WaSH) Working Group
- Given the multitude of interventions and strategies that fall within WaSH, the WaSH working group is subdivided into multiple subgroups.
- WaSH strategies sub-group: Ongoing work to identify specific WaSH interventions in various contexts including emergency response, ongoing preparedness, long-term interventions and integration with OCV campaigns.
 - Efficiency of WaSH interventions subgroup: Ongoing work to identify and develop an investment case methodology for WaSH interventions.
 - WaSH practices subgroup: Ongoing work to formulate recommendations for key WaSH practices to be implemented at the local level for cholera control.
 - Advocacy and funding subgroup: Ongoing work to identify evidence-based approaches, including essential personnel, materials and budget, to advocate for WaSH interventions in high cholera-risk areas.

2.5. Magnitude of the Problem of Cholera

Cholera is an acute watery diarrheal disease caused by the highly infectious facultative anaerobic Gram-negative, pathogenic, toxigenic bacterium *Vibrio cholerae* serogroups O1 and O139 belonging to the family *Vibrionaceae*. Humans are the only natural host for the pathogen. While there are more than 200 serogroups of *V. cholerae*, only two toxigenic ones, O1 and O139, are known to cause disease⁷. There is no known cross-protection between the O1 and O139 serogroups. The O139 serogroup first emerged as a cause of epidemics in 1992 in India and Bangladesh and accounted for ~2-9% of cases in Bangladesh for about a decade. China and Philippines recently reported cases of O139⁸, but overall cases seem confined to South and South-East Asia. The serogroup O1 has two biotypes – El Tor and classical. El Tor, the cause of the world’s seventh cholera pandemic, which began in 1961 and is still ongoing, has replaced classical strains, which are thought to have been responsible for the six previous pandemics in modern history. El Tor infections have a greater rate of asymptomatic or mild cases than the classical O1 – 75% of El Tor infections can be asymptomatic (vs. 59% for classical) and only 2% become severe as compared to an estimated 11% of infections with the classical biotype⁹. A new variant strain of *V. cholerae* O1 was identified in 2001¹⁰. This new strain identified is of the El Tor biotype, but it produces the cholera toxin formerly produced only by classical strains. These new variant strains appear to be predominant strains globally^{10,11}, are more virulent and cause more severe illness than the original El Tor strains^{12,13}. Both El Tor and classical biotypes of the O1 serogroup can further be classified into two serotypes – Ogawa and Inaba¹, and some degree of cross-protection occurs between the two serotypes, Ogawa and Inaba.

Transmission of pathogenic *V. cholerae* in humans occurs through ingestion of contaminated food and water. While only around 25% of persons infected develop symptoms (with an illness to infection ratio ranging from 1:3 to 1:100), 10-20% of those who do become symptomatic experience severe disease, after an incubation period of less than 24 hours to five days. The risk of severe illness is increased by the size of the dose ingested, the lack of immunity from prior exposure to the disease or through vaccination, reduced ability to produce gastric acid (which neutralizes the pathogen), and having blood group O.

Severe cholera (also referred to as cholera gravis) is characterized by profuse watery diarrhea (“rice water stools”) and usually vomiting, leading to rapid dehydration. Fluid loss can occur at a rapid rate of one-half to one liter per hour and if not promptly treated, the severe dehydration and resulting complications such as renal failure, shock, hypokalemia, and pulmonary edema can lead to death within hours. Unlike most other diarrheal diseases, cholera can be severe and even fatal in both adults and children. The symptoms of severe cholera are primarily due to the production of cholera toxin. The binding (B) subunit of the cholera toxin attaches to the mucosal surface of the intestine and releases the active (A) subunit, which enters the host cell. This activation of the cholera toxin results in a massive loss of fluids and electrolytes, especially sodium, potassium, and bicarbonate through the stool and vomitus. The stools and often the vomitus of these patients contain high concentrations of cholera vibrios, which can then contaminate water and food sources when passed back into the environment, with the potential for causing cholera outbreaks. Some studies also suggest that human colonization of *V. cholerae* creates a hyperinfectious state of the bacteria that is maintained soon after shedding, and that may contribute to the epidemic spread of the disease¹⁴.

¹ A third Hikojima strain has antigens of both types but is relatively unstable.

Cholera disease burden globally is characterized by both endemic disease and outbreaks/epidemics (described later in the section on surveillance). In addition, humanitarian emergency settings (both acute and chronic) are high-risk situations for cholera given large scale disruptions in water and sanitation infrastructure, population movements and security issues. The reported incidence of cholera has steadily increased since 2000, but the period from 2010 – 2014 saw a dramatic increase in incidence and case-fatality, mostly due to the large outbreak in Haiti and several outbreaks in sub-Saharan Africa^{8,15-18}. A cumulative total of 317,534 cases and 7543 deaths (2.38% case fatality rate), and 589,854 cases and 7816 deaths (1.3% case fatality rate) were reported to WHO in 2010 and 2011 respectively, representing an increase in incidence of 43% and 85% over previous years, and a 52% increase in the case fatality rate in 2010 compared with 2009. Although the reported numbers of cases and deaths decreased during the following years, they remain significantly higher than those in the early 2000s. The occurrence of cholera is also intrinsically related to major fluctuations in weather patterns, especially large scale rains as seen with the El Nino weather patterns¹⁹⁻²². Figure 1 shows the global burden of cholera cases and deaths from 2010 – 2015 as reported to WHO. Table 1 shows the case counts in several large-scale outbreaks reported since 2010.

A recent estimate showed that there were about 2.9 million cases of cholera annually in 69 cholera endemic countries and 95 000 deaths during 2008–2012²³. The same study also showed that sub-Saharan Africa accounted for 60% and south-east Asia accounted for 29% of the cholera cases. **It is to be noted that this represents the tip of the iceberg. Most mild to moderate cases do not seek care and several deaths occur in communities before reaching a health care facility which are often not reported. Additionally, many high-burden countries in southern Asia and sub-Saharan Africa do not report cases to WHO while some others report cases as ‘acute watery diarrhea’ and not cholera.** In particular, over 2 million acute watery diarrhea cases are registered in Bangladesh every year, of which an estimated 22% represent cholera cases¹⁸.

Figure 1: Global Cholera Cases and Deaths Reported to the World Health Organization, 2010 – 2015

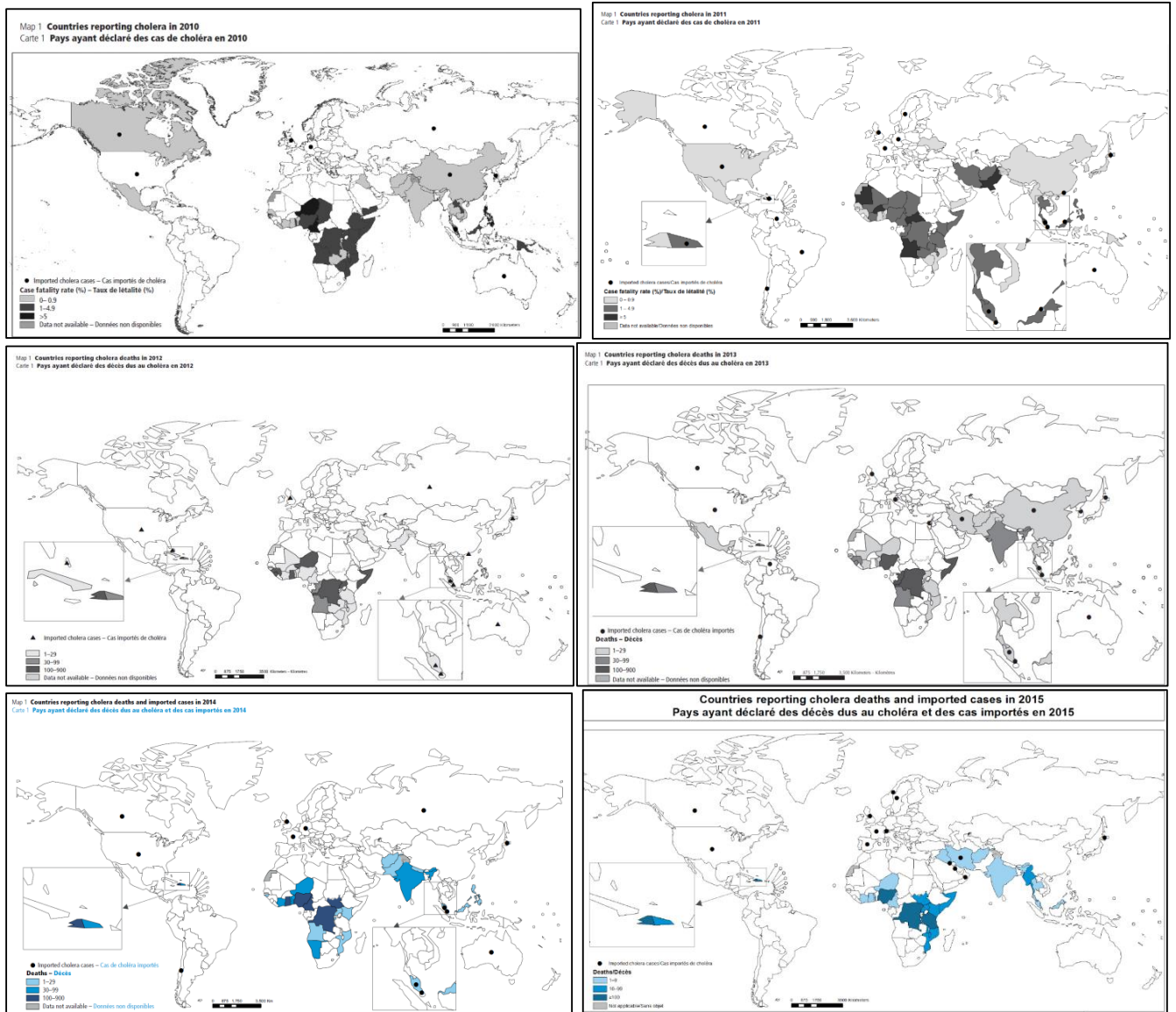


Table 1: Selected* Cholera Outbreaks Reported to the World Health Organization, 2010–2015

Year	Country (WHO Region)	Cumulative number of cases	Cumulative number of deaths	Case-fatality rate
2010–2015	Haiti (AMR)	754,972	8,863	1.2%
2015	Kenya (AFR)	13,291	67	0.5%
2015	Tanzania (AFR)	11,563	144	1.3%
2015	Iraq (EMR)	4,965	2	<0.1%
2014	Ghana (AFR)	28,944	243	0.8%
2014	Cameroon (AFR)	3,355	184	5.5%
2014	Democratic Republic of Congo (AFR)	22,203	372	1.7%
2014	Nigeria (AFR)	35,996	755	2.1%
2013	Angola (AFR)	6,655	86	1.3%
2013	Nigeria (AFR)	6,600	229	3.5%
2013	Somalia (AFR)	6,864	140	2.0%
2012	Democratic Republic of Congo (AFR)	33,661	819	2.5%
2012	Uganda (AFR)	6,326	135	2.0%
2012	Guinea (AFR)	7,350	133	1.8%
2012	Sierra Leone (AFR)	23,124	299	1.3%
2012	Ghana (AFR)	9,548	100	1.1%
2012	Angola (AFR)	1,215	98	8.1%
2012	Iraq (EMR)	4,693	4	0.1%
2012	Philippines (WPR)	1,864	14	0.8%
2011	Somalia (AFR)	77,636	1,130	1.5%
2011	Angola (AFR)	1,810	110	6.1%
2011	Chad (AFR)	17,267	458	2.7%
2011	Niger (AFR)	2,324	60	2.6%
2011	Nigeria (AFR)	23,377	742	3.2%
2011	Afghanistan (EMR)	3,733	44	1.2%
2011	Mali (AFR)	2,220	95	4.3%
2011	Cameroon (AFR)	22,433	783	3.5%
2010	Nigeria (AFR)	44,456	1,712	3.9%
2010	Chad (AFR)	6,395	175	2.7%
2010	Cameroon (AFR)	10,759	657	6.1%
2010	Niger (AFR)	1,154	66	5.7%
2010	Zambia (AFR)	6,794	62	1.0%
2010	Papua New Guinea (PNG) (WPR)	8,997	95	1.1%

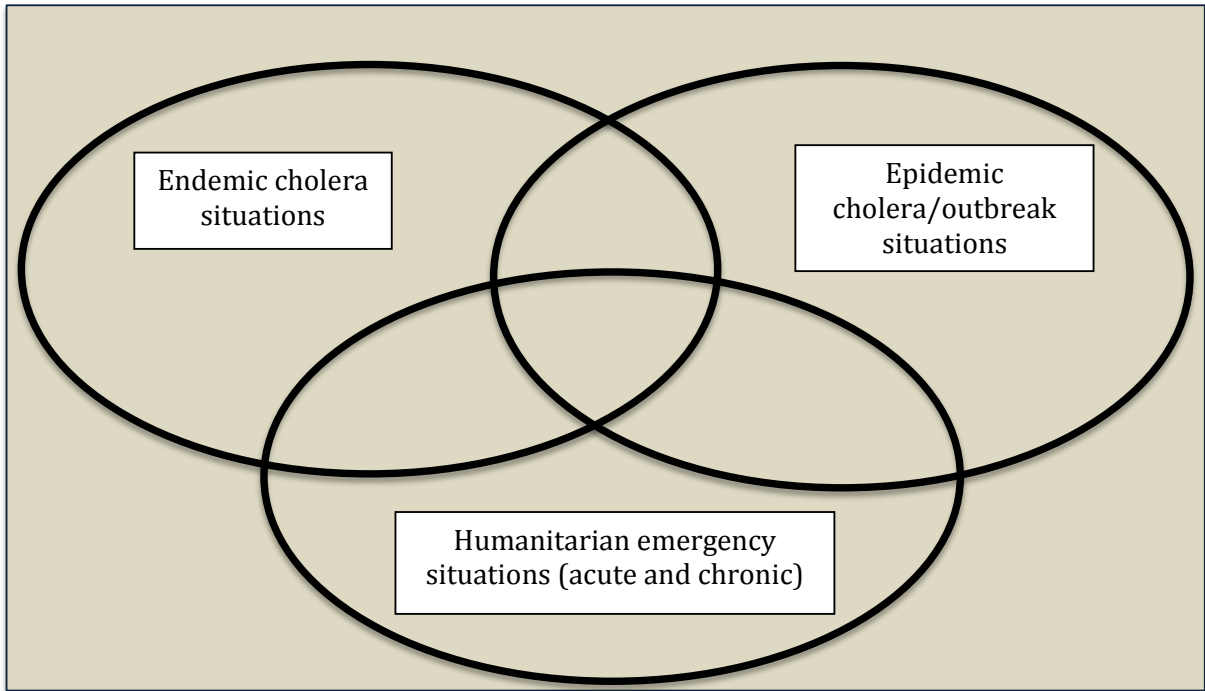
*Not a comprehensive list.

2.6. Cholera Surveillance – Epidemiology and Laboratory Components

Cholera surveillance is a critical component of a comprehensive cholera prevention and control strategy. Effective cholera surveillance entails use of standard case definitions, clear and simple data collections mechanisms, reporting and data analysis procedures, rapid diagnosis of suspected cases and laboratory confirmation, routine feedback of surveillance data, and appropriate coordination at all levels (community, health facility, district, national and international). However, in reality, most countries lack appropriate epidemiological systems and laboratory diagnostic capacity required for surveillance and rapid detection. Since 1962, WHO has been updating global cholera statistics based on cases reported to WHO by national health authorities, but is largely underreported as described earlier. Although notification of cholera cases is no longer mandatory under the current International Health Regulations (IHR) since 2005, WHO recommends assessment of cholera events against the IHR criteria to determine whether there is a need for official notification (<http://www.who.int/mediacentre/factsheets/fs107/en/>). For the most part, cholera is included within the National Integrated Disease Surveillance and Response (IDSR) or Early Warning and Response Network in humanitarian emergencies (EWARN) platforms. There are, however, numerous variations in case definitions, use of laboratory procedures and reporting mechanisms which impede standardized reporting and comparison of annual trends by region and globally. To address some of these issues, a multi-partner consortium supporting cholera surveillance and research – Africhol (The African Cholera Surveillance Network) was funded by the Bill and Melinda Gates Foundation in 9 African countries in 2009 by building upon and reinforcing existing surveillance systems and laboratory capacities.

Cholera disease burden is characterized by both endemic and epidemic disease, which in reality are two ends of a continuum. In addition, there are a number of situations that increase risk of both epidemic cholera as well as cause a resurgence of cases in already known endemic areas, for example, humanitarian emergency situations which may be acute or protracted crisis situations. Figure 2 illustrates the different cholera scenarios which overlap to a large extent. Biologically, a population is considered to have endemic cholera when there is existence of an environmental reservoir able to maintain infection in the area and does not depend on exogenous introduction²⁴. For practical purposes, endemic cholera is defined as the occurrence of fecal culture-confirmed cholera diarrhea in a population in at least 3 of the past 5 years⁵, and occurrence of cholera not meeting this definition would be regarded as 'epidemic'. These, however, do not take into account other factors such as water and sanitation conditions required for sustained transmission. Hence, there are vast differences in 'endemic cholera' occurrences in developed versus developing settings. Also, cholera surges in endemic situations usually trigger an epidemic response in terms of public health interventions. An additional term "cholera hotspots" has been used to identify highly endemic areas (frequent spikes in endemic cholera incidence) or areas where populations have a high risk of cholera transmission (e.g. areas with poor WaSH conditions). Exact technical definitions of endemic cholera, epidemic cholera, cholera alert, and cholera hotspots are under development through the 'Epidemiology and Surveillance Workgroup of the GTFCC' (Personal Communication, GTFCC Secretariat, WHO).

Figure 2: Cholera Scenarios



In addition to epidemiological surveillance, laboratory diagnostic capacity forms a critical component of cholera surveillance. Culture of fecal samples from patients remains the standard test for cholera confirmation, and a positive culture test from several patients is required for outbreak confirmation. Although relatively easy to perform, culture requires the availability of skilled personnel, laboratory facilities and sample transport mechanisms, which are not always available. More accurate techniques such as polymerase chain reaction (PCR) methods are becoming available, but require enhanced laboratory capacity. Alternatively, rapid diagnostic tests (RDTs) offer point-of-care diagnostic solutions, can be performed by semi-skilled personnel and can help with rapid detection and reporting in the absence of equipped laboratory facilities, especially in areas with poor health care access. A recent study found that use of a RDT with an enrichment step was equivalent to bacterial culture²⁵. Several types of RDTs are available with varying degrees of sensitivity, specificity, commercial readiness and precision in field conditions, and not all are suitable for use. The laboratory working group of the GTFCC is working on streamlining implementation and effective use of RDTs in the field.

Cholera surveillance guidance documents are under development through the epidemiology and surveillance and laboratory working groups of the GTFCC. A working document on cholera surveillance to inform and evaluate OCV use is available as part of the OCV stockpile monitoring and evaluation toolkit (http://www.who.int/cholera/vaccines/surveillance_protocol.pdf?ua=1). Also, a glossary of terms and case definitions has been developed under the Delivering Oral Vaccines Effectively (DOVE) Project at Johns Hopkins University which describes commonly used cholera terms, including surveillance (https://www.stopcholera.org/sites/cholera/files/1.2_glossary_of_cholera_terms.pdf).

2.7. Cholera Treatment

Rapid rehydration constitutes the primary treatment for cholera, either through oral rehydration therapy (ORT) or the administration of intravenous (IV) fluids to replace the loss of fluids and electrolytes, in more severe cases²⁶. Patients with no or moderate dehydration are usually treated with oral rehydration salts (ORS); WHO and UNICEF recommend a low osmolarity solution that reduces the incidence of vomiting over the original ORS formulation. The 10-20% of cholera patients who develop severe dehydration must be rehydrated rapidly with IV fluids, preferably Ringer's lactate solution, followed by ORT, once the patient is able to drink. Exact guidelines for management of diarrhea and dehydration and details of rehydration therapy are available through WHO (<http://www.who.int/cholera/en/>), UNICEF (https://www.unicef.org/cholera/index_71220.html) and other sources³.

WHO also recommends treatment with antibiotics for severe cases of cholera (http://www.who.int/cholera/prevention_control/Antibiotics_for_cholera_5March2014.pdf), since antibiotic therapy reduces the volume of diarrhea, the duration of illness and time spent in the hospital, as well as the length of time the pathogen is excreted in the stool, thereby potentially reducing transmission of the infection to others^{3,4}. WHO recommends doxycycline for treating cholera, with azithromycin as an alternative in areas known to have strains resistant to these first-line drugs (http://www.who.int/cholera/prevention_control/Antibiotics_for_cholera_5March2014.pdf). If patients have access to appropriate care for cholera, the case fatality rate should be minimal. Resistance to first-line antibiotics, as well as multiple-drug resistant (MDR) *V. cholerae*, is a frequent occurrence in cholera-endemic parts of the world and can complicate the treatment of cholera and increase treatment costs.

2.8. Cholera Prevention

Improving access to potable, clean water, adequate sanitation and promoting good hygiene practices (WaSH) remain the mainstays of preventing both endemic cholera and cholera outbreaks²⁷. Behavior change interventions to promote hand washing with soap, safe food handling, establishment and enforcement of basic sanitation laws for food industries, including food vendors are important interventions for cholera prevention. In addition, proper case management is vital in reducing mortality from the disease and limiting its spread²⁷.

Cholera vaccination is a key complementary cholera prevention and control strategy, which can be implemented in the short- to medium-term, while access to other primary prevention measures such as safe water and sanitation improves globally. WHO and the Global Taskforce for Cholera Control (GTFCC) calls for an integrated, comprehensive cholera control strategy which includes the primary WaSH strategies, case management and vaccination²⁸.

Additional information regarding WaSH is available through WHO (<http://www.who.int/cholera/publications/en/>), UNICEF (https://www.unicef.org/cholera/index_71218.html), and Centers for Disease Prevention and Control (<https://www.cdc.gov/cholera/six-messages.html>, <https://www.cdc.gov/cholera/training-education.html>).

3. Currently Available, Whole-cell (WC), Killed, Oral Cholera Vaccines (OCVs)

3.1. Key Points

- A new generation of whole-cell killed OCVs are available and have been shown to be safe, efficacious and effective in multiple settings.
- Four killed OCVs are available and licensed in different countries – Dukoral, mORCVAX, Shanchol and Euvichol. Of these, three vaccines – Dukoral, Shanchol and Euvichol are prequalified by WHO for procurement by United Nations agencies, such as UNICEF. mORCVAX is currently being produced and locally used in Vietnam. Other vaccine candidates are undergoing manufacturing processes through technology transfers to developing country manufacturers (e.g., Cholvax - Bangladesh), or are under development. An additional single dose, live attenuated OCV has been recently licensed in the United States for adult travelers.
- Herd protection (indirect protection afforded to unvaccinated individuals living in vaccinated areas) has been demonstrated with the current OCVs. This has the potential for increased impact on prevention of cholera transmission and reducing cholera morbidity and mortality.
- Use of OCVs, with established cholera prevention and control measures such as strengthening surveillance, rehydration, antibiotics, provision of safe water and adequate sanitation, and improved hygiene practices, provides a more integrated and comprehensive package of interventions for cholera control globally.
- A global OCV stockpile was established in 2013 and later supported by Gavi, the Vaccine Alliance. The Gavi-supported global OCV stockpile has successfully deployed over 7 million doses to 14 countries in a variety of contexts – humanitarian emergencies, outbreaks, and endemic hotspots.
- Increased demand has stimulated increased global OCV availability through increased production by existing and additional manufacturers at low costs.
- Coordination of governmental and nongovernmental partners by the Global Taskforce for Cholera Control has led to stronger collaborative efforts to support cholera prevention and control in endemic countries and epidemic and humanitarian crisis situations by incorporating disease surveillance, WaSH, case management and vaccines.

3.2. Details of the Available WC, Killed OCVs

Three WHO-prequalified, killed, whole-cell OCVs are currently available for global use² - Dukoral (killed whole cell monovalent (O1) vaccine with cholera toxin B subunit), and Shanchol and Euvichol (modified killed bivalent (O1 and O139) whole cell only vaccines).

² Other manufacturers in Vietnam and Bangladesh are producing similar OCVs, but are currently planned for national use only.

Vaccine prequalification is an activity led by the World Health Organization intended to ensure that vaccines purchased by UN procurement agencies meet WHO recommendations for quality, safety, and efficacy (http://www.who.int/immunization_standards/vaccine_quality/pg_system/en/).

Killed whole cell monovalent (O1) vaccine with cholera toxin B subunit (WC-BS and WC-rBS)

Dukoral was developed in Sweden (SBL Vaccin, Sweden) and first licensed in 1991. It contains a mixture of the recombinant B subunit (BS) of cholera toxin plus formalin and heat killed whole cells (WC) strains of *V. cholerae* O1 (monovalent) representing serotypes Inaba and Ogawa and biotypes El Tor and Classical. The B subunit of cholera toxin was originally produced chemically (WC-BS), but is now produced by recombinant technology (WC-rBS), but both BS and rBS are identical in terms of immune response⁵. This is to be noted as some of the earlier vaccine studies used the WC-BS formulation of the vaccine. The vaccine does not contain any of the cholera toxin A subunit and is free of its toxic effects. Because the heat labile toxin (LT) of *E. coli* cross reacts with cholera toxin, this vaccine has been shown to provide short term cross protection against diarrhoea caused by enterotoxigenic *E. coli*²⁹. The vaccine requires two doses for adults and three doses for children below five years of age. The vaccine requires co-administration of a bicarbonate buffer in safe water to prevent degradation of the toxin B subunit. In Bangladesh, a placebo controlled randomized controlled trial (RCT) in 90,000 individuals aged 2 years and above demonstrated 85% efficacy for 6 months following vaccination and 50% efficacy of 3 years for older children and adults³⁰. In Beira, Mozambique, mass vaccination was feasible and effective in preventing cholera in a population with a 20–30% seroprevalence of HIV^{31,32}. More than 14,000 people received a least one dose and a case control study demonstrated 78% protection against cholera and 89% protection against cholera with severe dehydration³². Of note, all strains isolated in this evaluation were El Tor variants that produced a modified form of the classical cholera toxin, representing a newer, dominant, and more severe variety of cholera. Though WHO prequalified, it has mainly been used as a travellers' vaccine due to limited production, higher price, and relative difficulty for public health use given the need for higher cold chain volume and clean water requirement for reconstitution of the buffer.

Modified killed whole cell only vaccines (WC)

On the basis of the encouraging findings of the use of WC-rBS vaccine, the technology for production of the oral killed whole cell vaccine was transferred from Sweden to Vietnam in the 1980s. The Vietnamese government commenced local development of an inexpensive oral O1 serogroup whole cell only vaccine in the 1980s. This vaccine was similar in composition to WC-rBS except it lacked the B subunit toxin. It was shown to be safe and conferred 66% protection against cholera during an epidemic which occurred 8-10 months following vaccination in an open field trial³³. The vaccine was made into a bivalent formulation (O1 and O139) and was licensed as mORCVAX (Vabiotech, Hanoi, Vietnam) in 1997. Because the vaccine lacks toxin, it does not require co-administration with an oral buffer. Over 20 million doses were used in Vietnam's public health programs. Unfortunately, this vaccine was not suitable for WHO prequalification as the Vietnamese national regulatory authority (NRA) was not assessed as WHO functional, a condition for pre-qualification, and Good Manufacturing Practice (GMP) considerations. International scientists worked together to improve vaccine constituents and the manufacturing process, and transferred the modified vaccine to India, which had a functional NRA approved by the WHO.

The resulting vaccine, Shanchol (Shantha Biotechnics Ltd, India; now Sanofi Pasteur), was prequalified by WHO in 2011. It was shown to be well tolerated and highly immunogenic in multiple highly endemic and less endemic settings in Vietnam, India, and Ethiopia³⁴⁻³⁷. Shanchol has conferred 67% protection in a double blind randomized placebo controlled trial in more than 67,000 children and adults in Kolkata, India^{38,39}. However, levels of protection were not uniform across all age groups. Young children aged one to five years, were significantly less protected with a cumulative efficacy of 42% over 5 years³⁹. A large community based feasibility and effectiveness trial with over 267,000 participants in Bangladesh showed that in real life settings in a highly mobile urban community, a population based vaccination program achieving moderate coverage in hyperendemic settings could substantially reduce the burden of disease and greatly contribute to long term cholera control⁴⁰. When comparing responses between one and two vaccine doses, investigators from Kolkata found no increase in seroconversion (4 fold rise in serum vibriocidal antibodies), following a second dose as compared to those after the first dose⁴¹. Interestingly, this may be directly related to the amount of natural exposure and pre-existing antibodies since higher seroconversion rates were noted following a second dose in comparatively less endemic areas in Haiti and Ethiopia³⁷. This suggests that there may be important geographical differences in immunological response in areas of varying cholera exposure. A study in Kolkata compared the immunogenicity of two dosing regimens (14 vs. 28 days apart) and found no difference in the immunogenicity⁴². A phase 3 placebo RCT assessing a single dose of Shanchol in over 200,000 individuals from the hyperendemic setting of Bangladesh found an efficacy of 40% against all cholera cases and 60% protective against cholera cases with severe dehydration over a 6-month period⁴³. A recent study in Haiti showed that HIV-infected individuals developed somewhat lower but still appreciable serum vibriocidal antibody responses compared with those in HIV-uninfected individuals, and that among HIV-infected persons, the magnitude of these responses varied inversely with CD4 lymphocyte counts⁴⁴.

Similar to Shanchol, Euvichol (Eubiologics, South Korea) is the second affordable OCV which resulted from development of the Vietnamese vaccine. Euvichol was prequalified by WHO in late 2015. It has the same formulation as Shanchol and clinical studies have demonstrated immunological non-inferiority when compared with Shanchol⁴⁵. The entry of Euvichol into the market in 2016 is expected to significantly increase vaccine availability and potential use.

Similar non-inferiority evaluations are underway for another formulation of the whole cell, killed OCV - Cholvax (Incepta, Bangladesh). Once complete, the aim is to increase production capacity, enabling vaccination of large populations at risk in Bangladesh. Similar to the situation with mORCVAX in Vietnam, the Bangladesh NRA is not currently approved by WHO and Cholvax is expected to be available for local use in Bangladesh.

A summary of key characteristics and features of the currently available WC, killed OCVs are presented in Table 2.

Table 2. Key characteristics and features of the currently available killed OCVs (WC-rBS and Modified WC), as of March 2017

Generic Name	WC-rBS	Modified Bivalent WC
Trade Name	Dukoral	mORCVAX (Vietnam), Shanchol (India), Euvichol (Korea), Cholvax (Bangladesh)
Target	O1 (Classical, El Tor – Ogawa and Inaba) Cholera toxin B subunit	O1 (Classical, ElTor – Ogawa and Inaba), O139 No cholera toxin
Regimen	2 doses given 2-6 weeks apart 3 doses for children 2 - 5 years	2 doses given 14 days (or 28 days) apart
Duration of protection	2 years (6 months for children 2-5 years of age)	5 years (Data >5 years is not available)
Age range for vaccination	≥2 years	mORCVAX: ≥2 years others: ≥1 year
Requirement for oral buffer	Yes (bicarbonate buffer in 75 – 150 ml water)	No
Storage temperature	2-8°C	2-8°C ^ç
Shelf life	3 years (36 months) at 2-8°C	30 months at 2-8°C
WHO Prequalification status	WHO prequalified	WHO prequalified - Shanchol and Euvichol
Price to the public sector (per dose)	\$5.25	mORCVAX: \$0.75 Shanchol/Euvichol: \$1.85
Comments	Licensed in more than 50 countries worldwide	Euvichol plans to use squeezable plastic tubes for easier administration
Projected supply ^µ	Figure 6	Figure 6

* Preclinical testing complete and Phase I/II studies being initiated in Bangladesh

ç Shanchol: growing evidence for stability at elevated temperature (42°C) and the safety/ immunogenicity profiles are not altered.

£ Enterocoating of rBS is expected to allow for storage at 30-37°C, but needs to be evaluated

µ Current projections of OCV supply are based on planned replenishment into the stockpile, which is divided into an emergency stock (outbreaks and humanitarian emergencies) and non-emergency reserve (endemic hotspots).

A systematic review of post-licensure deployment of OCVs was published in 2014 and lists experiences with OCV use in multiple endemic, epidemic and humanitarian emergency settings until 2013⁴⁶. Figure 2 shows the different post licensure OCV campaigns during 1997–2014.

Since the establishment of the OCV stockpile in 2013 until March 2017, a total of 41 OCV campaigns have been conducted in 14 countries through OCV stockpile deployments.

Figure 3: Post-licensure Oral Cholera Vaccine Campaigns, 1997–2014

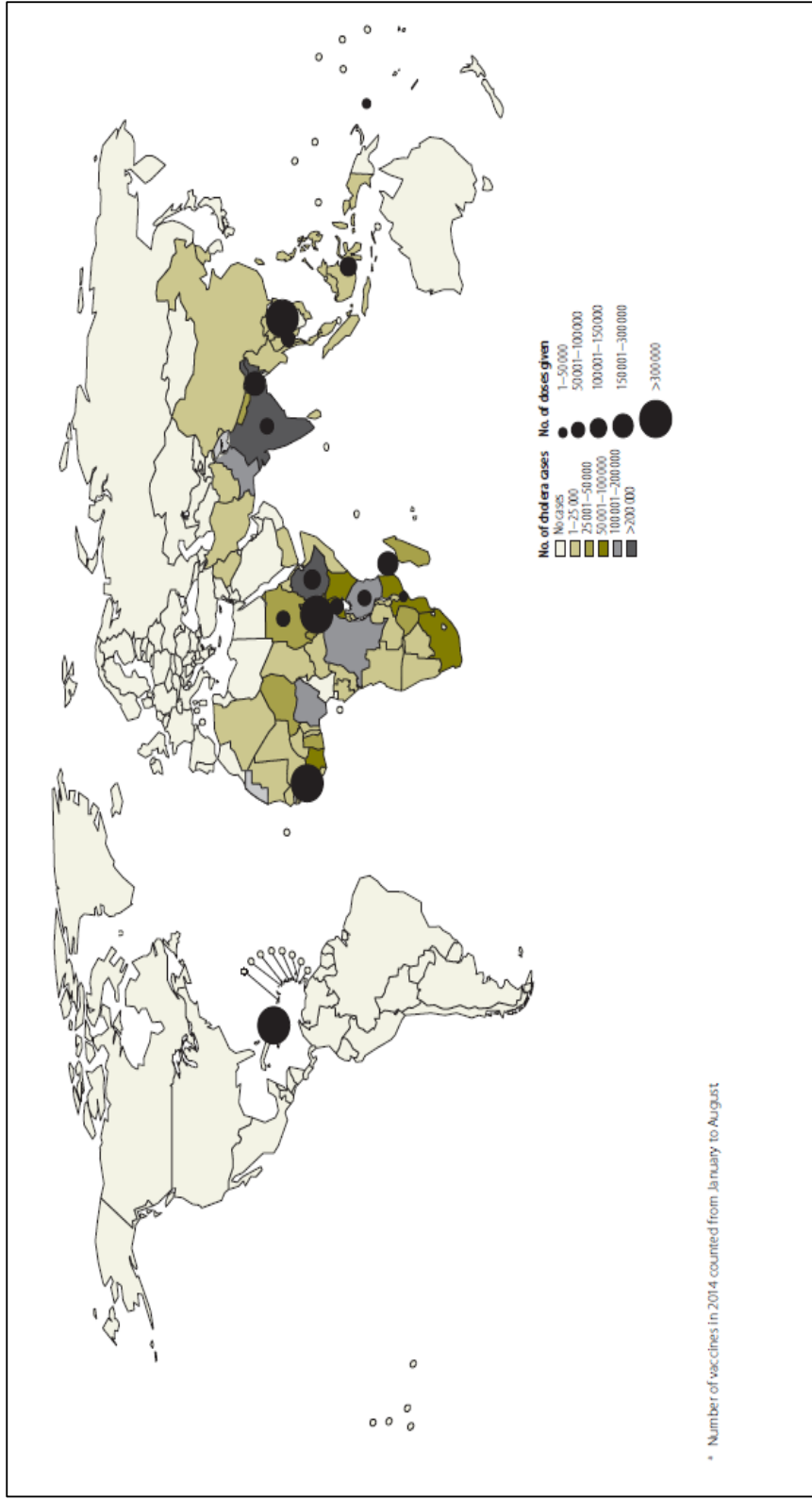


Table 3 lists experiences with OCV use in large-scale phase 3 clinical trials and post-licensure use to date (as of March 2017) including costs and coverage, where available (Preliminary List).

Vaccine & Campaign year	Site	Setting	Target population	No. or doses delivered or Coverage	Costs
Dukoral, 1997	Uganda (Adjumani district) ^{47,48}	Stable refugee camp, rural Preemptive campaign	44,000	1 st dose - 35,613 (81%) 2 nd dose - 27,607 (62%)	Vaccine – free (by manufacturer) Local delivery - \$0.53 per person
Dukoral, 2000	Comoros (Mayotte Island) ⁴⁶	Urban and rural, Preemptive campaign	145,000	2 doses – 93,000 (64%)	Not available
Dukoral, 2003 – 2004	Mozambique (Beira) ^{31,32,49,50}	Urban	19,550	1 st dose – 14,164 (72%) 2 nd dose – 11,070 (57%)	Vaccine – free (by manufacturer) Local delivery - \$2.01 per person
Dukoral, 2004	Sudan (South Darfur) ⁵¹	Refugee camp (acute crisis), rural Preemptive campaign	45,825	1 st dose – 45,502 (93%) 2 nd dose – 40,330 (88%)	\$7.1 per person Local delivery - \$0.7 per person
Dukoral, 2005	Indonesia (Aceh) ⁵¹	Internally displaced persons sites, post-tsunami	78,870	1 st dose – 65,505 (79%) 2 nd dose - 54,627 (69%)	\$17.55 Local delivery – \$3.10 per person
Dukoral, 2009	Tanzania (Zanzibar) ⁵²⁻⁵⁸	Urban and rural Preemptive vaccination in an endemic area with seasonal outbreaks	48,178	1 st dose – 27,678 (57%) 2 nd dose – 23,921 (50%)	\$31.46 Local delivery – 3.66 per person
ORCVAX/mORCVAX, 1998 - 2012	Vietnam ⁵⁹	Preemptive and reactive vaccination of children (2 – 5 years old) integrated into Vietnam’s public health program	~10.9 million	Not available	Not available

Vaccine & Campaign year	Site	Setting	Target population	No. or doses delivered or Coverage	Costs
ORCVAX/mORCVAX, 1998, 2000, 2013	Vietnam (Hue) ^{50,59,61}	Preemptive vaccination in a cholera endemic area	149,557 (1998) 137,082 (2000)	1998: 1 st dose – 125,135 (84%), 2 nd dose – 118,703 (79%) 2000: 1 st dose – 104,706 (76%), 2 nd dose – 103,226 (75%)	1998: \$0.89 per person 2013: \$1.07 per person
ORCVAX/mORCVAX, 2008	Vietnam (Hanoi)	Reactive vaccination during an outbreak	~370,000	~80% (details not available)	Not available (likely similar to the costs of the other use in Vietnam due to similar procurement and delivery mechanisms)
Shanchol, 2006	India (Kolkata) ⁶²	Urban slum Randomized controlled efficacy trial	52,212 (Vaccine group)	2 doses: 33,127 (63%)	Not available/applicable. Clinical trial setting.
Shanchol, 2011	India (Odisha) ⁶³⁻⁶⁶	Rural Preemptive campaign	51,488	1 st dose – 31,552 (61%) 2 nd dose – 23,751 (46%)	\$6.30 Local delivery costs – \$1.13
Shanchol, 2011	Bangladesh (Dhaka) ^{40,67,68}	Urban slum Cluster randomized trial with 3 arms (vaccine, vaccine+ WaSH, no intervention)	172,754	1 st dose – 141,839 (82%) 2 nd dose – 123,666 (72%)	\$3.93 (vaccine cost was subsidized by manufacturer) Local delivery - \$1.63
Shanchol, 2012	Haiti (Port-au-Prince) ^{69,70}	Urban slum Reactive vaccination in a protracted outbreak situation	70,000	1 st dose – 52,357 (75%) 2 nd dose – 47,540 (68%)	Not available
Shanchol, 2012	Haiti (Bocozel and Grand Saline) ^{44,71-74}	Rural Reactive vaccination in a protracted outbreak situation	~50,000	1 st dose – 45,417 2 nd dose – 41,238 (77 – 79% in Bocozel and 63% in Grand Saline)	Not available

Vaccine & Campaign year	Site	Setting	Target population	No. or doses delivered or Coverage	Costs
Shanchol, 2012	Solomon Islands (Choiseul and Shortland provinces) ^{46,75}	Rural Preemptive campaign in an area (cholera naïve setting) near a cholera outbreak in Papua New Guinea	~15,000 Children 1 – 15 years old.	1 st dose – 11888, 2 nd dose - 11318	Not available
Shanchol, 2012	Guinea (Boffa and Forecariah) ⁷⁶⁻⁷⁹	Rural Reactive vaccination during an ongoing outbreak.	~209,000	1 st dose - 172,544 2 nd dose – 143,706. Administrative coverage = 68% in Boffa and 51% in Forecariah. Coverage survey – 76%	\$6.37 Local delivery costs - \$1.97
Shanchol, 2013	Thailand (Tak Province – Thailand Myanmar border) ⁸⁰	Rural Stable refugee camp	43,968	1 st dose – 36,325 (83%) 2 nd dose – 26,753 (61%)	~\$8.39 Local delivery costs - \$2.45 (personal communication, CDC preliminary results)
Shanchol, 2013	South Sudan (Maban County) ⁴⁶	Rural Refugee camps – preemptive vaccination.	146,317	2 doses – 132,000 Coverage survey – 85%	\$15.06 Local delivery costs – \$3.99
Shanchol, 2013	Haiti (Petite Anse and Cerca Carvajal) ⁸¹	Urban and Rural Preemptive vaccination campaign – first OCV campaign by the Haitian Ministry of Health Some vaccine also used in prisons (documentation in process)	~107,906	Administrative coverage: 92% in Petite Anse and 104% in Cerca Carvajal. Coverage survey: 77% (rural – Cerca Carvajal), 63% (urban – Petite Anse)	\$2.9 per dose administered. Local delivery costs - \$0.70 per dose administered (note this data is per dose administered and not per person as indicated in earlier reports). (CDC personal communication – Manuscript in Press – Routh et al.)

Vaccine & Campaign year	Site	Setting	Target population	No. or doses delivered or Coverage	Costs
Shanchol, 2014	South Sudan ^{82,84}	Internally displaced persons' camps. Humanitarian crisis First use of global OCV stockpile	162,577	Coverage estimates (administrative and LQAS) 1) Toning camp (Juba): 1 st dose 94%, 2 nd dose 93% 2) UN house camp (Juba): 1 st dose 96%, 2 nd dose 95% 3) Mingkaman camp (Awerial): 1 st dose 82%, 2 nd dose 64% 4) Bor camp (Bor): 1 st dose 92%, 2 nd dose 86% 5) Bentiu camp: not available 6) Malakal camp: 1 st dose 97%, 2 nd dose 92%	Local delivery costs obtained from the 2 NGOs that delivered vaccine \$0.63 and \$0.73 per vaccine dose (note: the cost is per vaccine dose and not per person).
Shanchol, 2014	Haiti	Urban and rural – seven communes in three departments (Artibonite, Centre, Ouest)	185,314	2-dose OCV coverage (coverage survey) Artibonite – 70% (LBCL 60%) Centre – 63% (LBCL 55%) Ouest – 44% (LBCL 35%) (Burnett et al – Manuscript in preparation)	Not available
Shanchol, 2015	Malawi (Nsanje district) ⁸⁵	Rural Reactive campaign in an area affected by flooding and a cholera outbreak	160,482	Administrative coverage 1 st round: 97.6% 2 nd round: 85.8% 2 dose coverage – 67.6%	Not available
Shanchol, 2015	Malawi (Chikwawa)	Rural Humanitarian crisis	12,415	Not available	Not available

Vaccine & Campaign year	Site	Setting	Target population	No. or doses delivered or Coverage	Costs
Shanchol, 2015	Iraq (Nationwide in IDP camps) ⁸⁶	Reactive campaign following an outbreak. Preemptive campaign in some areas at high risk. IDP and refugee camps, collective centers. Protracted humanitarian crisis	255,000	Coverage survey 2-dose coverage: 87%. Coverage was lower in the South and Central Governorates	Not available
Shanchol, 2015	Zambia (Lusaka)	Reactive campaign using a single dose. Urban - Lusaka	578,000	2-dose coverage = 68.6% (coverage survey)	Not available
Shanchol, 2015	Tanzania (Kigoma)	Rural Humanitarian crisis – camps	246,874	Not available	Not available
Shanchol, 2015	Nepal (Nuwakhot and Dhanding)	Outbreak - urban Post-crisis (post-earthquake)	10,486	2-dose coverage = 98.1% (coverage survey)	Not available
Shanchol, 2015	Cameroon (Mokola, Hina)	Rural Humanitarian crisis	56,044	102% (administrative)	Not available
Shanchol, 2016	Niger (Diffa region)	Rural Humanitarian crisis	98,024	At least one dose = 86.5% (administrative coverage)	Not available
Shanchol, 2016	Haiti (Archaie)	Urban – endemic	118,097	96.7% (administrative)	Not available
Shanchol, 2016	Malawi (Lake Chilwa area)	Rural – outbreak	100,000	Coverage survey 1-dose coverage – 83% 2-dose coverage – 69%	Not available
Shanchol, 2016	South Sudan (Wau Shuluk and Melut IDP)	Rural Humanitarian crisis	36,000	Not available	Not available

Vaccine & Campaign year	Site	Setting	Target population	No. or doses delivered or Coverage	Costs
Shanchol, 2016	Democratic Republic of Congo (Kinshasa)	Urban – high risk areas	375,640	Administrative coverage – 1 st dose round = 94% Data on 2 dose coverage not available.	Not available
Euvichol, 2016	Haiti (Sud and Grand Anse)	Humanitarian crisis Hurricane affected areas. Single dose campaign.	820,000	Administrative coverage Sud = 90% Grand Anse = 96%	Not available
Euvichol, 2017	South Sudan	Outbreak setting	68,967	Administrative coverage for Round 1 – 44%	Not available

3.3. Scientific Evidence Review

In the following sections, the different key characteristics of the available, killed, whole cell OCVs and related evidence are described. This information has been used to develop the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework for evidence review and recommendations for use of the killed, whole cell OCVs. The GRADE Review is described in subsequent sections.

A) Vaccine Safety

Table 4 below lists the key randomized control trials (RCTs) for OCV that have evaluated ‘safety’ as one of the outcome measures.

In addition, there are a number of evaluations of the programmatic use of OCVs that have evaluated safety, and the findings have been consistent with the findings of the RCTs listed below.

Table 4: Summary of the key publications related to safety of the currently available, killed OCVs

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Concha et al. Bull Pan Am Health Organ, 1995	1992	Colombia	1,165 healthy individuals between 12 months and 64 years of age.	2 doses of WC-rBS; heat killed <i>E. coli</i> K12 placebo	Randomized, double blind, placebo controlled trial (RCT)	No significant bias	Few symptoms detected during the 3 days following administration of the initial dose and even fewer followed the second dose two weeks later.	
Trach DD et al. Bull WHO, 2002	2002	Vietnam	Trial 1: 144 healthy adults randomized to receive bivalent WC vaccine with or without buffer, WC-rBS vaccine with buffer, or placebo without buffer. Trial 2: 103 healthy children 1 – 12 years randomized to bivalent WC vaccine without buffer, WC-rBS vaccine with buffer or placebo without buffer.	2 doses of bivalent WC vaccine, WC-rBS vaccine, placebo	Randomized controlled trial (RCT)	No significant bias	No significant difference in AEs between any vaccine groups compared with placebo among children and adults. Almost all reported AEs were mild (fever, diarrhoea, abdominal pain, loss of appetite, nausea)	

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Anh DD et al, Vaccine 2007	2005	Vietnam	144 Healthy male and non-pregnant females aged 18 – 40 years old (74 vaccine, 70 placebo)	2 doses of reformulated bivalent WC vaccine; heat-killed <i>E. coli</i> K12 placebo	Randomized, double blind, placebo controlled trial	No significant bias	No significant difference in AEs between the vaccine and the placebo groups. No serious AEs were detected. Reported AEs included diarrhoea, abdominal pain, nausea, vomiting, fever, headache and general ill feeling	Subjects with history of diarrhoea, anti-diarrheal treatment or antibiotics during the past week, and history of diarrhoea and abdominal pain lasting 2 weeks during the prior 6 months were excluded.
Mahanabalis et al. PlosOne, 2008.	2006	India	101 healthy individuals (including non-pregnant females) 18 – 40 years old, and 100 children 1 – 17 years old. Non-pregnant female participants.	2 doses of reformulated modified WC-BS vaccine before tech transfer.	Randomized placebo controlled safety and immunogenicity trial (RCT)	No significant bias	No significant difference in AEs between the vaccine and placebo groups.	First study of the reformulated Vietnamese vaccine prior to the technology transfer outside of Vietnam.
Sur et al. Lancet, 2009	2006	India	Individuals ≥ 1 year old, non-pregnant. 31,932 individuals (1721 clusters) received 2 doses of vaccine and 34968 individuals (1757 clusters) received 2 doses of placebo.	2 doses of Shanchol; heat killed <i>E. coli</i> K12 placebo	Cluster-randomised double blind, placebo controlled trial (RCT)	No significant bias	No statistically significant difference in AEs between intervention and control groups. 105 participant reported AEs – 51 were deemed to be serious, 36 (vaccine 18, placebo 18) were admitted to the hospital (most common cause – acute gastroenteritis – 24/36). 15 deaths (vaccine 6, placebo 9).	
Saha et al, Vaccine 2011	2010	Bangladesh	Health adults (18–45 years), toddlers (2–5 years) and younger children (12–23 months) 110 participants in each age group (55 vaccine and 55 placebo)	2 doses of Shanchol	Double blind randomized placebo controlled trial (RCT)	No significant bias	No significant difference in AEs in any age group between vaccine and placebo recipients.	
Qadri et al. Lancet 2015	2011	Bangladesh	90 clusters in urban Dhaka slums; ~270,000 persons (95115 – vaccination only; 93091 vaccination + behaviour change + 80690 – no intervention)	2 doses of Shanchol; 2 doses of Shanchol+ behaviour change; no intervention	Cluster randomized controlled trial (RCT)	No significant bias	A total of 95 adverse events (AEs) were recorded. (44 vaccination grp, 51 in vaccination and behaviour change group) – all mild AEs No serious adverse event recorded.	
Desai et al, JIE, 2014	2012 - 2013	Ethiopia	Healthy adults (aged 18 years and above) and children (aged 1–17 years). 216 participants (54 adults+ 54 children in each group)	2 doses of Shanchol 14 days apart; non-biological placebo	Individually randomized, double-blind, placebo-controlled trial (RCT)	No significant bias	No difference in adverse events between vaccine and placebo groups. No adverse event (AE) in the vaccine group. 1 AE in the placebo group – mild. No serious adverse event.	Not a highly endemic setting. Similar baseline characteristics between groups.

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Baik, et al. Vaccine, 2015	2014	Philippines	Healthy adults (aged 18–40 years) and children (aged 1–17 years) randomized into two groups (Euvichol: 388 Adults, 240 children. Shanchol: 389 Adults, 244 children).	2 doses of Euvichol, 2 doses of Shanchol	Individually randomized controlled, multi-center, non-inferiority trial (RCT)	No significant bias	AEs – 4.4% Euvichol, 6.9% Shanchol. No difference between the two vaccines and between age groups. All mild (headache, fever – most common) No serious adverse events.	Non-inferiority trial comparing Euvichol and Shanchol.
Qadri et al. NEMJ, 2016	2014	Bangladesh	Persons ≥1 year old, not severely ill, non-pregnant (Vaccine: 102,552 Placebo: 102,148)	Single dose of Shanchol	Individually randomized, placebo controlled trial (RCT).	No significant bias	No difference in adverse events between the vaccine and placebo group. No difference in serious adverse events.	Follow-up ongoing

B) Vaccine Efficacy (and Immunogenicity studies)

Table 5 below lists the key OCV studies that have evaluated 'vaccine efficacy' as one of the outcome measures. The table also includes immunogenicity studies which corroborate the efficacy findings.

Table 5: Summary of the key publications related to efficacy of the currently available, killed OCVs

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Clemens et al. Lancet 1990	1985 - 1989	Bangladesh (Matlab)	Children 2 - 15 years old and women 16 years and older (3 doses at 6 weeks interval); 62,285 completed 3 doses (total - 89,596)	WC-rBS and WC only vaccines	Randomized double blind, placebo controlled trial	No significant bias	Protective efficacy: 4 - 6 months: all ages - 85% (LBCL 56%); 2 - 5 y/o - 100% (LBCL 80%) 1 year: all ages - 62% (LBCL 50%); 2 - 5 y/o - 38% (LBCL 7%) 2 years: all ages - 58% (LBCL 44%); 2 - 5 y/o - 47% (LBCL 13%) 3 years: all ages - 18% (LBCL -14%); 2 - 5 y/o - nil	Rapidly waning immunity after 2 years. Two doses were found to be as effective as 3 doses except in the 2 - 5 year olds.
Sanchez et al. Lancet, 1994	1994	Peru	Military recruits 16 - 45 years old (1,426 participants)	2 doses of WC-rBS given 7 - 27 days apart	Randomized, double blind placebo controlled trial	No significant bias	Protective efficacy - 86% (LBCL 37%).	
Taylor et al. JID 2000	1994 - 1995	Peru (outskirts of Lima)	2 - 65 years old persons 17,799 received 2 doses (14,997 received a booster dose)	2 doses of WC-rBS given 2 weeks apart, booster dose given 10 months after 2 nd dose	Randomized, double blind placebo controlled trial	First year results excluded due to methodological problems	After 2 years the protective efficacy against clinical cholera was 61% (LBCL = 28%). Vaccine efficacy was higher for persons >15 years old: 72% (95% CI 28-89). VE against illness requiring hospitalization was 82% (95% CI 27-96).	
Trach et al. Lancet 1997	1992 - 1993	Vietnam (Hue)	134,453 persons - vaccine and no vaccine groups (no placebo and not randomized); 51,975 completed the 2-dose regimen.	2 doses of ORCVAX (bivalent WC)	Large scale, open field trial	No randomization. No placebo - trial not masked. Study period short compared with cholera trends in Hue. Inclusion vaccine refusers in the control group. Potential differential migration of participants outside the study area.	Protective efficacy over 10 months All ages - 66% (LBCL 46%) Children 1 - 5 years old 68% (LBCL 14%)	

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Sur et al. Lancet, 2009	2006	India	Individuals ≥ 1 year old, non-pregnant. 31,932 individuals (1721 clusters) received 2 doses of vaccine and 34968 individuals (1757 clusters) received 2 doses of placebo.	2 doses of Shanchol	Cluster-randomised double blind, placebo controlled trial; heat killed <i>E. coli</i> K12 placebo	No significant bias. Study not powered to distinguish levels of protection by year between year 1 and 2.	<p><u>2-year efficacy data</u> Adjusted protective efficacy = 67% (LBCL=35%) – all ages.</p> <p><u>By age group</u></p> <ol style="list-style-type: none"> 1–4 y/o: 49% (LBCL=6%) 5–14 y/o: 87% (LBCL=54%) ≥ 15 y/o: 63% (LBCL=23%) <p><u>By year</u></p> <p>Year 1: 45% (LBCL -5%) Year 2: 72% (LBCL 49%)</p>	
Bhattacharya et al, Lancet, 2013	2006	India	Individuals ≥ 1 year old, non-pregnant. 31,932 individuals (1721 clusters) received 2 doses of vaccine and 34968 individuals (1757 clusters) received 2 doses of placebo.	2 doses of Shanchol	Cluster-randomised double blind, placebo controlled trial; heat killed <i>E. coli</i> K12 placebo	No significant bias. Substantial increase in protective efficacy during year 5 (likely due to a large cholera outbreak during year 5, which may have boosted natural immunity in the population). High endemic areas – potential natural immunity boosting.	<p><u>5-year Efficacy data (per protocol analysis)</u> Adjusted cumulative protective efficacy = 65% (LBCL 52%)</p> <p><u>By age group</u></p> <ol style="list-style-type: none"> 1–4 y/o: 42% (LBCL=5%) 5–14 y/o: 68% (LBCL=42%) ≥ 15 y/o: 74% (LBCL=58%) <p><u>By year of follow-up</u></p> <p>Year 1: 48% (LBCL -11%) Year 2: 78% (LBCL 52%) Year 3: 67% (LBCL 41%) Year 4: 57% (LBCL 26%) Year 5: 80% (LBCL 40%)</p>	Point estimates by year of follow-up suggested no evidence of decline in protective efficacy. Results did not vary significantly between per protocol analysis and intent to treat analysis.
Saha et al. Vaccine, 2011	2010	Bangladesh	Health adults (18–45 years), toddlers (2–5 years) and younger children (12–23 months) 110 participants in each age group (55 vaccine and 55 placebo)	2 doses of Shanchol	Double blind randomized placebo controlled trial (RCT)	No significant bias	Vibriocidal antibody responses in adults were 60% against <i>Vibrio cholerae</i> O1 Inaba, 72% against <i>V. cholerae</i> O1 Ogawa and 21% against <i>V. cholerae</i> O139. In toddlers, responses were 84%, 75% and 64% and in younger children it was 74%, 78% and 54% against Inaba, Ogawa and O139 serotypes. The responses in all ages were higher in vaccines compared to pre-immune titers or to responses in placebo recipients ($P < 0.001$).	

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Desai SN et al. AJTMH, 2015	2012 – 2013	Ethiopia	Healthy adults (aged 18 years and above) and children (aged 1–17 years). 216 participants (54 adults+ 54 children in each group)	2 doses of Shanchol 14 days apart; non-biological placebo	Individually randomized, double-blind, placebo-controlled trial (RCT) – immunogenicity bridging trial	No significant limitations or biases. Direct comparison with other trials not possible due to protocol differences and lack of standardization of vibriocidal titres.	Seroconversion against O1 Inaba after 2 doses: 53% (1 – 5 y/o), 89% (6 – 17 y/o), 81% (adults) Seroconversion against O1 Ogawa after 2 doses: 75% (1 – 5 y/o), 90% (6 – 17 y/o), 70% (adults) In general, seroconversion was lower after the 1 st dose.	Less endemic setting. Similar baseline characteristics between groups. Vaccine less immunogenic after the 1 st dose.
Qadri et al. NEJM, 2016	2014	Bangladesh	Persons ≥1 year old, not severely ill, non-pregnant (Vaccine: 102,552 Placebo: 102,148)	Single dose of Shanchol	Individually randomized, placebo controlled trial (RCT) Passive surveillance for cholera.	6 month duration of protection assessed. Individual randomization – indirect effect not captured.	Protective efficacy=40% (LBCL*=11%) for any cholera, all ages, 63% (LBCL=24%) for severely dehydrating cholera, all ages. <u>By age group</u> 1) 1 – 4 y/o: any cholera 16% (LBCL* = -50%), severe 28% (LBCL = -221%) 2) 5 – 14 y/o: 63% any cholera (LBCL=-39%), severe 84% (-36%) 3) ≥15 y/o: 56% any cholera (LBCL=16%), 64% severe (LBCL=10%)	No protection in younger age groups. Follow-up ongoing.
Baik et al. Vaccine, 2015	2014	Philippines	Healthy adults (aged 18–40 years) and children (aged 1–17 years) randomized into two groups (Euvichol: 388 Adults, 240 children. Shanchol: 389 Adults, 244 children).	2 doses of Euvichol, 2 doses of Shanchol	Individually randomized controlled, multi-center, non-inferiority trial (RCT)	No significant limitations or biases	Euvichol seroconversion against O1 Inaba after 2 doses: 87.4% (1 – 17 y/o), 81.7% (Adults) Euvichol seroconversion against O1 Ogawa after 2 doses: 90.5% (1 – 17 y/o), 80.1% (Adults) Shanchol seroconversion against O1 Inaba after 2 doses: 88.9% (1 – 17 y/o), 76.3% (Adults) Shanchol seroconversion against O1 Ogawa after 2 doses: 88.1% (1 – 17 y/o), 73.9% (Adults)	Non-inferiority trial comparing Euvichol and Shanchol. Data in the youngest age groups not separately described.

*LBCL – Lower bound of the 95% confidence limit

C) Vaccine Field Effectiveness

Table 6 below lists the key studies that have evaluated 'vaccine field effectiveness' as one of the outcome measures. The findings of these studies align with the efficacy findings.

Table 6: Summary of the key publications related to field effectiveness of the currently available, killed OCVs

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Lucas et al. NEJM, 2005.	2004	Mozambique (Beira)	Study included 43 cases and matched 172 controls (High HIV seroprevalence setting of 20 – 30%)	2 doses of WC-rBS vaccine (3 doses in children)	Observational case control study	No randomization. (however bias indicator study included and shows no bias)	78% protection, 1 – 6 months after vaccination (95% CI: 39 – 92%, p=0.004). Vaccine was equally effective in children <5 years old	High HIV prevalence in the area.
Khatib et al. Lancet Inf Dis, 2012	2009 - 2010	Tanzania (Zanzibar)	Of 48,178 eligible individuals, 23,921 received vaccine in 2009. Outbreak occurred in the area during 2009 – 2010.	2 doses of WC-rBS (Dukoral)	Observational Prospective cohort study. Health facility based diarrhoea surveillance	No randomization. (Bias indicator study suggests absence of any significant bias) Differences between vaccine recipients and non-recipients (gender, access to tap water).	Direct protection 79% (LBCL 47%) Indirect (herd) protection was shown by a decrease in the risk for cholera of non-vaccinated residents within a household's neighborhood as the vaccine coverage in that neighborhood increased.	
Wierzba et al. Vaccine, 2015	2011	India (Odisha)	145 villages, ~50,000 population. Healthy, non-pregnant, ≥1 year old	2 doses of Shanchol	Observational study (case-control test negative design)	Some baseline differences between cases and controls. Test negative design. Potential selection bias factors among cases and controls.	Adjusted VE = 69% (LBCL* : 14.5%) Cohort analysis VE=70% (LBCL=48%)	Field implementation or feasibility study. Includes bias indicator analysis. Age specific estimates not available.

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Qadri et al. Lancet, 2015	2011	Bangladesh	90 clusters in urban Dhaka slums; ~270,000 persons (95,115 – vaccination only; 93,091 vaccination + behaviour change + 80,690 – no intervention)	2 doses of Shanchol; 2 doses of Shanchol + behaviour change; no intervention	Cluster-randomized controlled trial (RCT) Passive cholera surveillance.	No significant bias (bias indicator study included)	<u>Vaccination only group (overall protection)</u> Adjusted VE = 37% (LBCL=13%) <u>By age group:</u> 1) 1 – 4 y/o = 52% (LBCL= –4%) 2) 5 – 14 y/o = 33% (LBCL= –88%) 3) ≥15 y/o = 34% (LBCL=6%) <u>Vaccination + behaviour change group</u> Adjusted VE = 45% (LBCL=19%) <u>By age group:</u> 1) 1 – 4 y/o = 23% (LBCL= –65%) 2) 5 – 14 y/o = 41% (LBCL= –70%) 3) ≥15 y/o = 49% (LBCL=23%) The adjusted cumulative 2-year total protection was 53% (95% CI lower bound 34%; p=0 • 0001) in the vaccination only group and 58% (95% CI lower bound 41%; p<0 • 0001) in the vaccination and behavioral change group	Cluster randomized field effectiveness (phase 4 trial).
Ivers et al. Lancet Global Health, 2015	2012 - 2014	Haiti	Target population: ~45,417 persons vaccinated in Rural Haiti. Reactive vaccination in a protracted outbreak setting.	2 doses of Shanchol	Observational – case control study with bias indicator study	No significant bias (bias indicator study included) Vaccination status assessed mainly through verbal reporting; fewer could be validated by card or registry	In multivariable analyses, vaccine effectiveness was 63% (95% CI 8–85) by self-report and 58% (13–80) for vaccination verified through the card or registry. By age group: VE among children <5 years old = 50% (LBCL= –85). Time since vaccination: VE within 1 year = 87%, ≥ 1 year = 64%.	
Severe et al. AJTMH, 2016	2012 - 2015	Haiti (urban slum)	~70,000 persons in urban slums of Port-au-Prince, Haiti; nearby comparison area which was not vaccinated	2 doses of Shanchol	Observational study Cholera surveillance data from one CTC. VE = (ARU – ARV)/ARU x 100 – attack rates in unvaccinated and vaccinated individuals	Several limitations in data analysis and interpretation	VE estimated to be 97.5% in the vaccinated area compared with unvaccinated area.	Combined WaSH and vaccine related interventions

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Luquero et al. NEJM. 2014	2012	Guinea	Nonselective mass vaccination campaigns were implemented in the prefectures of Boffa and Forécariah.	2 doses of Shanchol with an interval of at least 2 weeks	Observational matched case-control study with bias indicator study	No significant bias (bias indicator study included) Small sample size, but power remained high. Potential differences in health seeking behaviour may exist, but this bias is assumed to be small.	2 doses provided at effectiveness measure of 86.6% (56.7-95.8) for all ages. Incomplete dose effectiveness measure: 42.8% (-83.6-82.2)	
Azman et al. Lancet Global Health, 2016	2015	South Sudan	165 000 people were vaccinated with a single dose of oral cholera vaccine in this campaign, which targeted high risk areas of Juba	1 dose of Shanchol	Observational – case-cohort study with bias indicator study	No significant bias (bias indicator study included) Small sample size, which impede to estimate direct vaccine effectiveness through classical matched case-control design. Vaccination status assessed through verbal reporting and vaccination card; 50% could be validated by card or registry	In multivariable analyses, vaccine effectiveness was 87.3% (70.2–100.0).	In press, should be available in the next few weeks

* LBCI= Lower bound of the 95% confidence limit

E) Duration of Protection

Table 7 below lists the key studies that have evaluated 'duration of protection' as one of the outcome measures. Data is available on duration of protection for up to 5 years for a multidose schedule and up to 6 months for a single dose schedule.

Table 7: Summary of the key publications related to duration of protection of the currently available, WC killed OCVs

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
van Loon et al, Vaccine, 1996.	1985 - 1989	Bangladesh (Matlab)	Children 2 – 15 years old and women 16 years and older (3 doses at 6 weeks interval); 62,285 completed 3 doses (total – 89,596)	WC-BS and WC only vaccines; placebo	Randomized double blind, placebo controlled trial	No significant bias	During 5 years of follow-up, there were 144 cases of cholera in the WC-BS group (PE = 49%; P < 0.001), 150 in the WC group (PE = 47%; P < 0.001), and 283 in the placebo group. Protection by each vaccine was evident only during the first three years of follow-up; long-term protection of young children was observed only against classical but not El Tor cholera; 3-year protection against both cholera biotypes occurred among older persons, but at a higher level against classical cholera.	
Thiem et al, Vaccine 2006	1998 - 2000	Vietnam (Hue)	Mass immunization of children and adults with the killed whole-cell oral cholera vaccine was undertaken in half of the communes of Hue, Vietnam, in 1998; the remaining communes were immunized in 2000. In all, 48 confirmed and 21 suspected cases matched to 192 and 84 controls were included.	ORCVAX and mORCVAX	Observational case-control study	No significant bias (bias indicator study included). Inclusion of suspected cases, self-reported vaccination status, small sample size.	No cholera was observed in Hue until 2003, when an outbreak of El Tor cholera made it possible to conduct a case-control study. The overall vaccine effectiveness 3-5 years after vaccination was 50% (95% CI 9-63).	

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Bhattacharya et al, Lancet, 2013	2006	India (Kolkata)	Individuals ≥ 1 year old, non-pregnant. 31,932 individuals (1721 clusters) received 2 doses of vaccine and 34968 individuals (1757 clusters) received 2 doses of placebo.	2 doses of Shanchol	Cluster-randomised double blind, placebo controlled trial; heat killed <i>E. coli</i> K12 placebo	No significant bias. Substantial increase in protective efficacy during year 5 (likely due to a large cholera outbreak during year 5, which may have boosted natural immunity in the population). High endemic areas – potential natural immunity boosting.	5-year Efficacy data (per protocol analysis) Adjusted cumulative protective efficacy = 65% (LBCL 52%) By age group 4. 1–4 y/o: 42% (LBCL=5%) 5. 5–14 y/o: 68% (LBCL=42%) 6. ≥ 15 y/o: 74% (LBCL=58%) By year of follow-up Year 1: 48% (LBCL -11%) Year 2: 78% (LBCL 52%) Year 3: 67% (LBCL 41%) Year 4: 57% (LBCL 26%) Year 5: 80% (LBCL 40%)	Point estimates by year of follow-up suggested no evidence of decline in protective efficacy. Results did not vary significantly between per protocol analysis and intent to treat analysis.
Khatib et al, Lancet Inf Dis, 2012	2009 - 2010	Tanzania (Zanzibar)	Of 48,178 eligible individuals, 23,921 received vaccine in 2009. Outbreak occurred in the area during 2009–2010.	2 doses of WC-rBS (Dukoral)	Observational Prospective cohort study. Health facility based diarrhoea surveillance	No randomization. (Bias indicator study suggests absence of any significant bias) Differences between vaccine recipients and non-recipients (gender, access to tap water).	For 15 months duration, direct protection 79% (LBCL 47%). Indirect (herd) protection was shown by a decrease in the risk for cholera of non-vaccinated residents within a household's neighborhood as the vaccine coverage in that neighborhood increased.	
Wierzba et al, Vaccine, 2015	2011	India (Odisha)	145 villages, ~50,000 population. Healthy, non-pregnant, ≥ 1 year old	2 doses of Shanchol	Observational study (case-control test negative design)	Some baseline differences between cases and controls. Test negative design. Potential selection bias Potential difference in risk factors among cases and controls.	Adjusted VE = 69% (LBCL *: 14.5%) for approximately 1 year duration. Cohort analysis VE=70% (LBCL=48%)	Field implementation on or feasibility study. Includes bias indicator analysis. Age specific estimates not available.

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Ivers et al. Lancet Global Health, 2015	2012 - 2014	Haiti	Target population: ~45,417 persons vaccinated in Rural Haiti. Reactive vaccination in a protracted outbreak setting.	2 doses of Shanchol	Observational – case control study with bias indicator study	No significant bias (bias indicator study included) Vaccination status assessed mainly through verbal reporting; fewer could be validated by card or registry	Time since vaccination: VE within 1 year = 87%, ≥ 1 year = 64%. In multivariable analyses, vaccine effectiveness was 63% (95% CI 8–85) by self-report and 58% (13–80) for vaccination verified through the card or registry. By age group: VE among children <5 years old = 50% (LBCL=-850).	
Severe et al. AJTMH, 2016	2012 - 2015	Haiti (urban slum)	~70,000 persons in urban slums of Port-au-Prince, Haiti; nearby comparison area which was not vaccinated	2 doses of Shanchol	Observational study Cholera surveillance data from one CTC. VE = (ARU – ARV)/ARU x 100) – attack rates in unvaccinated and vaccinated individuals	Several limitations in data analysis and interpretation	VE estimated to be 97.5% in the vaccinated area compared with unvaccinated are at 37 months.	Combined WaSH and vaccine related interventions

F) Indirect Protection (Herd Protection)

Vaccine-induced herd effects are described in terms of herd immunity and herd protection, and these two terms are often used interchangeably⁸⁷. Herd immunity is generally used to describe the protection of non-vaccinated people exposed to live vaccine organisms transmitted by shedding of these organisms by vaccinees, leading to a protective immune response such as with oral polio vaccine, whereas herd protection refers to reduction in the intensity of transmission of the organism as a result of the presence of vaccinated individuals in the community. Consideration of herd protection thus forms an important aspect of vaccines under consideration for population-level use due to several factors, 1) cost-effectiveness of vaccines, 2) vaccine coverage as needed for adequate disease control, 3) microorganism strain replacement⁸⁷.

Table 8 lists the key studies that have evaluated herd protection effects of the currently available, WC, killed OCVs.

Table 8: Summary of the key publications related to herd protection of the currently available, WC killed OCVs

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Ali et al, Lancet 2005 ⁸⁸	1985 - 1989	Bangladesh (Matlab)	Children 2 – 15 years old and women 16 years and older (3 doses at 6 weeks interval); 62,285 completed 3 doses (total – 89,596)	WC-BS and WC only vaccines; placebo	Randomized double blind, placebo controlled trial A reanalysis of the original trial data		Vaccine coverage of the targeted population ranged from 4% to 65%. Incidence rates of cholera among placebo recipients were inversely related to levels of vaccine coverage (7.01 cases per 1000 in the lowest quintile of coverage vs 1.47 cases per 1000 in the highest quintile; $p < 0.0001$ for trend). Receipt of vaccine by an individual and the level of vaccine coverage of the individual's cluster were independently related to a reduced risk of cholera. After adjustment for the level of vaccine coverage of the cluster, vaccine protective efficacy remained significant (55% [95% CI 41–66], $p < 0.0001$).	This was a reanalysis of the 1985 – 1989 trial data.
Khatib et al, Lancet Inf Dis, 2012 ²⁵	2009 - 2010	Tanzania (Zanzibar)	Of 48,178 eligible individuals, 23,921 received vaccine in 2009. Outbreak occurred in the area during 2009 – 2010.	2 doses of WC-RBS (Dukoral)	Observational Prospective cohort study. Health facility based diarrhoea surveillance	No randomization. (Bias indicator study suggests absence of any significant bias) Differences between vaccine recipients and non-recipients (gender, access to tap water).	Direct protection 79% (LBCI 47%) Indirect (herd) protection was shown by a decrease in the risk for cholera of non-vaccinated residents within a household's neighborhood as the vaccine coverage in that neighborhood increased.	

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Ali et al. CID, 89 2013	2006	India (Kolkata)	Individuals ≥ 1 year old, non-pregnant. 31,932 individuals (1721 clusters) received 2 doses of vaccine and 34968 individuals (1757 clusters) received 2 doses of placebo.	2 doses of Shanchol	Cluster-randomised double blind, placebo controlled trial; heat killed <i>E. coli</i> K12 placebo In the cluster design, herd protection was assessed by comparing the incidence of cholera among participants in vaccine clusters versus those in placebo clusters. In the geographic information system (GIS) analysis, herd protection was assessed by evaluating association between vaccine coverage among the population residing within 250 meters of the household and occurrence of cholera in that population.		In the cluster design, the 3-year data showed significant total protection (66% protection [95% confidence interval: 50-78%]; $p < 0.01$), but no evidence of indirect protection. With the GIS approach, the risk of cholera among placebo recipients was inversely related to neighborhood-level vaccine coverage, and the trend was highly significant ($p < 0.01$). This relationship held in multivariable models that also controlled for potentially confounding demographic variables (hazard ratio: 0.94 [95% confidence interval: 0.90-0.98]; $p < 0.01$). Overall, herd protection was evident in analyses using the GIS approach, but not the cluster design approach, likely due to considerable transmission of cholera between clusters.	

G) Dosing Interval (Alternative Schedule and Booster Regimen)

Table 9 lists the key studies that have evaluated an alternative schedule and booster regimen for the currently available WC, killed OCVs.

Table 9: Summary of the key publications related an alternative schedule and booster regimen of the currently available, killed OCVs

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Kanungo S, PlosNTDs, 2015 ⁴²	2012	India (Kolkata)	356 healthy, non-pregnant individuals \geq 1 year old randomized to receive the vaccine 14 and 28 days apart.	2 doses of Shanchol using two different regimens (14 days apart and 28 days apart).	Randomized controlled, double blind non-inferiority trial.	No significant bias.	Among adults, no significant differences were noted when comparing the rates of seroconversion for <i>V. cholerae</i> O1 Inaba following two dose regimens administered at a 14 day interval (55%) vs the 28 day interval (58%). Similarly, no differences in seroconversion were demonstrated in children comparing the 14 (80%) and 28 day intervals (77%). Following 14 and 28 day dosing intervals, vibriocidal response rates against <i>V. cholerae</i> O1 Ogawa were 45% and 49% in adults and 73% and 72% in children respectively.	Evidence of clinical protection needed
Kanungo S, PlosNTDs, 2015 ⁹⁰	2012	India (Kolkata)	426 healthy, non-pregnant participants, who were not diagnosed with cholera during the 5 year surveillance period	2 dose booster regimen of Shanchol 5 years after the primary 2-dose series	Nested, open label controlled trial among participants previously enrolled in the 2006 efficacy trial. Endpoints were compared between two intervention groups: a boosted population (individuals who received vaccine five years prior and were redosed) and a primary series population (participants who were placebo recipients in the original RCT and were receiving vaccine for the first time. Both of these groups received vaccine at days 0 and 14 and blood were drawn for measurement of vibriocidal titers. A third blood sample was also drawn on day 28 to compare baseline with titers 14 days following doses one and two.	No significant bias.	Among participants receiving a two dose primary series of OCV (n = 186), 69% (95% CI 62%-76%) seroconverted. In the intervention arm (n = 184), 66% (95% CI 59%-73%) seroconverted following a two dose boosting schedule given five years following the initial series. Following a single boosting dose, 71% (95% CI 64%-77%) seroconverted. Children demonstrated 79% (95% CI 69%-86%) and 82% (95% CI 73%-88%) seroconversion after primary and boosting regimens, respectively.	Evidence of clinical protection needed

H) Knowledge, Attitudes and Practices (KAP) Studies

As discussions occurred for inclusion of OCVs into a comprehensive cholera prevention and control package, concerns were expressed regarding the lack of data on any potential synergies vs. interference between vaccination and traditional cholera prevention and control measures. A few studies were conducted which assessed knowledge, attitudes and practices regarding cholera, WaSH and OCVs before and after OCV campaigns and the role of health education and messaging, and are summarized below in Table 10.

Table 10: Summary of selected studies that assessed knowledge, attitudes and practices regarding cholera, WaSH and OCVs, 2010 – current

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Albana et al. PLoSNTDs, 2013	2012	Haiti (Rural – Bocozel)	Rural Community where a reactive vaccination was conducted (protracted outbreak).	~50,000 individuals ≥ 1 year old, not pregnant	Baseline surveys on knowledge and practice relevant to cholera and waterborne disease to every 10th household during a census in rural Haiti in February 2012 (N = 811). An OCV campaign occurred from May-June 2012 after identical surveys to 518 households randomly chosen from the same region in September 2012. We compared responses pre- and post- OCV campaign.	Effect of other factors/interventions cannot be excluded. Self-reported water treatment and hygiene behaviours. Survey timings (different times of the year – which may influence WaSH behaviours)	Significant improvement in cholera knowledge and practices related to waterborne disease prevention noted at 3 months post-campaign as compared with before the campaign. Post-vaccination, there was improved knowledge with significant increase in percentage of respondents with ≥ 3 correct responses on cholera transmission mechanisms (odds ratio OR] 1.91; 95% confidence interval [CI] 1.52-2.40), preventive methods (OR 1.83; 95% CI 1.46-2.30), and water treatment modalities (OR 2.75; 95% CI 2.16-3.50). Relative to pre-vaccination, participants were more likely post-OCV to report always treating water (OR 1.62; 95% CI 1.28-2.05). Respondents were also more likely to report hand washing with soap and water >4 times daily post-vaccine (OR 1.30; 95% CI 1.03-1.64). Knowledge of treating water as a cholera prevention measure was associated with practice of always treating water (OR 1.47; 95% CI 1.14-1.89). Post-vaccination, knowledge was associated with frequent hand washing (OR 2.47; 95% CI 1.35-4.51).	The campaign incorporated a strong WaSH messaging component. NGO has a strong presence and community-level activities in the area.
Wahed et al. BMC Public Health, 2013	2010	Bangladesh (Dhaka)	Urban slum Dhaka In the setting of a large phase 4 clinical trial	Cluster randomized trial with 3 arms (vaccine, vaccine+ WaSH, no intervention)	Quantitative knowledge, attitudes and practices (KAP survey) and in-depth interviews before the trial.	No comparison point for after the campaign. Self-reported behaviours.	Of 2,830 families, 23% could recognize cholera as acute watery diarrhea and 16% had ever heard of oral cholera vaccine. About 54% of the respondents had poor knowledge about cholera-related issues while 97% had a positive attitude toward cholera and oral cholera vaccine. 1/3 rd showed poor practice relating to the prevention of cholera. The findings showed a significant (p < 0.05) association between the respondents' knowledge and sex, education, occupation, monthly overall household expenditure, attitudes and practice. In the adjusted model, male sex, having a lower monthly overall household expenditure, and having a less positive attitude toward cholera were the significant predictors to having poor knowledge.	Evaluated KAPs to inform messaging during the campaign

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Burnett et al. PlosNTDs, 2013	2012	Solomon Islands	Rural	~15,000 children 1 – 15 years old were vaccinated in areas adjacent to an outbreak	Quantitative KAP survey in areas targeted and not targeted for vaccination after the OCV campaign.	Comparability of the vaccinated and unvaccinated groups. Self-reported behaviours	Respondents in vaccinated areas were more likely to have received cholera education in the previous 6 months (33% v. 9%; $p = 0.04$), to know signs and symptoms (64% vs. 22%; $p = 0.02$) and treatment (96% vs. 50%; $p = 0.02$) of cholera, and to be aware of cholera vaccine (48% vs. 14%; $p = 0.02$). There were no differences in water, sanitation, and hygiene practices.	Cholera naïve setting
Peprah et al, Vaccine, 2016	2014	South Sudan	IDP camps Humanitarian crisis	162,577 persons targeted for vaccination.	Qualitative study semi-structured interviews 4 months after the campaigns	Potential recall issues (study occurred 4 months after vaccination). Limited generalizability.	Reasons for partial and non-acceptance of the vaccination included lack of time and fear of side effects, similar to reasons found in OCV campaigns in non-crisis settings. In addition, distrust in national institutions in a context of fears of ethnic persecution was an important reason for hesitancy and refusal. Other reasons included fear of taking the vaccine alongside other medication or with alcohol. The findings highlight the importance of considering the target populations' perceptions of institutions in the delivery of OCV interventions in humanitarian contexts. They also suggest a need for better communication about the vaccine, its side effects and interactions with other substances.	
Childs et al, AJTMH, 2016	2013	Haiti	Urban Rural	~107,906 persons were targeted for vaccination.	KAP survey was conducted both pre-campaign and post-campaign. Interviewer observation of the household to assess availability of water/water storage was also conducted.	The timing of the survey may have led to inaccurate results (cholera had become endemic). Most outcomes were self-reported behaviours (social desirability or recall bias). Different groups sampled pre and post the campaign. No control area/group	No significant differences in knowledge about causes, symptoms, and prevention of cholera were noted. However, treatment of drinking water significantly decreased along with safe storage of drinking water. These findings highlight the need for future campaigns to include a strong educational component that emphasizes the importance of maintaining appropriate WASH practices for the prevention of cholera and other diarrheal diseases even after vaccination, and highlights the limited effectiveness and duration of protection of OCV.	

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Scobie et al, PlosNTDs, 2016	2013 - 2014	Thailand	Refugee camp (long standing)	~43,485 persons were targeted for vaccination.	KAP cross-sectional surveys conducted 1 month before and 3 and 12 months after an OCV campaign.	High proportion of non-responding households (non-response bias). Self-report (social desirability or recall bias) Potential issues with accurate translation of questionnaire into all dialects spoken in camp	Compared with baseline, statistically significant differences were noted at first and second follow-up among the proportions of respondents who correctly identified two or more means of cholera prevention (62% versus 78% and 80%), reported boiling or treating drinking water (19% versus 44% and 69%), and washing hands with soap (66% versus 77% and 85%); a significant difference was also observed in the proportion of households with soap available at handwashing areas (84% versus 90% and 95%). Therefore, OCV campaigns may provide opportunities to reinforce beneficial WASH-related KAPs for prevention and control.	High migration rates

I) Note regarding the costing and cost-effectiveness of OCVs

Costs associated with the different OCV campaigns, including local delivery costs, are included in Table 3 earlier in the document.

A cost-benefit comparison of investments in improved water supply and cholera vaccination community-based programs showed, though, that improved water supply interventions and a targeted cholera vaccination program were much more likely to yield attractive cost-benefit outcomes than a community-based vaccination program alone ⁹¹.

Using the example of the 2008-2009 cholera outbreak in Zimbabwe, a retrospective cost-effectiveness analysis calculated the health and economic burden with and without a hypothetical reactive oral cholera vaccination. The primary outcome measure was incremental cost per disability-adjusted life year (DALY) averted. Under the base assumptions (50% vaccine coverage among individuals aged ≥ 2 years), reactive vaccination could have averted 1,320 deaths and 23,650 DALYs. Considering herd immunity, the corresponding values would have 2,920 deaths and 52,360 DALYs averted. Total vaccination costs were estimated to be about US\$74 million and \$21 million, respectively, with per-dose vaccine price of US\$5 and \$1. Assuming herd immunity, the corresponding cost was US\$980 with vaccine price of US\$5, and the program was cost-saving with a vaccine price of US\$1. The study concluded that reactive vaccination has the potential to be a cost-effective measure to contain cholera outbreaks in countries at high risk ⁹².

A more recent study describing the organization, vaccine coverage, and delivery costs of mass vaccination with a new, less expensive oral cholera vaccine using existing public health infrastructure in Odisha, India, demonstrated the affordability of vaccine and delivery costs for resource-poor countries. Vaccine cost at market price (about US\$1.85/dose) was the costliest item. The vaccine delivery cost was \$0.49 per dose or \$1.13 per fully vaccinated person ⁶⁵. Although the study noted that without cholera incidence data, it was not possible to estimate the Odisha-specific cost-effectiveness of vaccination, it did cite results from a cholera vaccination economic model using incidence estimates for other high-risk populations in India ⁶⁵. Assuming cholera vaccine coverage to be at 80% and 50% of measles vaccine coverage for populations 1-14 years and 15+ years, respectively, in the Southeast Asia region, a cost effectiveness ratio of \$785 per DALY averted for programs targeted to ages 1 year and above was estimated ¹.

J) Note regarding vaccine impact on disease transmission and trends

Most OCV studies to date have focused on vaccine safety, immunogenicity, effectiveness, coverage, behavioral aspects (knowledge, attitudes and practices), and economic aspects of OCV use, and there are very limited data on impact of OCV use on disease transmission and trends. Several modeling studies have estimated potential vaccine impact in multiple settings with different assumptions, including vaccination strategy, coverage and allocation ⁹²⁻⁹⁶ but data on actual impact remain limited.

A study in South Sudan has recently shown some promising results on vaccine impact ⁹⁷. Following mass population displacements in South Sudan, preventive cholera vaccination campaigns were conducted

in 6 displaced persons camps in 2014, but not in the surrounding host communities. In April 2014, two months after vaccine deployment, South Sudan confirmed the first case of cholera in the country, and over 5 months, 6,269 suspected cholera cases were reported, including 156 deaths. Most cases occurred outside vaccinated camps, mainly in communities or camps surrounding vaccinated populations. The epidemic curves within vaccinated camps in Juba had no distinct peak and suggested a series of cholera introductions with little to no onward transmission, whereas estimates in unvaccinated areas showed that despite conditions that may have been less suitable for transmission, transmission occurred for a sufficient and significantly longer time for an epidemic to progress.

More data on actual impact of OCVs on disease transmission and trends are needed in different epidemic and endemic settings.

K) Note on heat stability of the killed whole cell OCVs

Maintenance of cold chain (2 – 8 °C) is currently required for OCVs. However, new data are emerging on the thermostability of the vaccines, which is likely to greatly simplify delivery logistics – similar to the meningococcal A conjugate vaccine following use the controlled temperature chain (CTC) recommendations (<http://www.who.int/biologicals/areas/vaccines/controlledtemperaturechain/en/>).

A study conducted in Bangladesh showed that the safety and immunogenicity profile of Shanchol was maintained when stored at elevated temperatures of up to 42 °C for 14 days⁹⁸. In 2012, in an outbreak response vaccination campaign in Guinea, vaccine was maintained in cold chain during storage but transported and use at ambient temperatures during vaccination days⁷⁸. Following this campaign, the 2-dose OCV regimen was shown to be 86% effective⁷⁷.

The available killed OCVs are good candidates for CTC use and if approved, will help improve storage and delivery logistics, especially in resource-limited settings where cholera usually occurs.

L) Note on coadministration of OCVs with other vaccines

In general, concomitant administration of multiple vaccines, including live attenuated immunizations, is safe and effective. Some restrictions apply for live vaccines – administering a live-virus vaccine within 4 weeks after administration of another live-virus vaccine can decrease immunogenicity to the second administered vaccine, hence it is recommended that live-virus vaccines should be administered the same day or ≥4 weeks apart. Studies of oral polio vaccine and oral rotavirus vaccines, also both live viral vaccines, have shown decreased seroconversion for rotavirus, with the 1st dose, which was subsequently overcome after completion of the three-dose series⁹⁹. Data on coadministration of the currently available whole-cell killed OCVs with other oral vaccines, specifically, oral polio vaccines is lacking. Although the risk of immunological interference due to co-administration of live with non-live vaccines is considered small, if at all any, it has raised a theoretical concern of interference. The manufacturer of Shanchol has recommended a gap of 15 days between Shanchol and OPV given the lack of such data and the emphasis on global polio eradication (Letter issued by Shantha Biotechnics, 2011).

Specifically the WHO polio vaccine position paper (2016)¹⁰⁰ states that the limited available evidence supports the safety and immunogenicity of co-administration of OPV and oral cholera vaccines¹⁰¹. The WHO position paper on oral polio vaccines states that both oral and injectable polio vaccines can be coadministered with other vaccines.

A study is planned to specifically evaluate immunogenicity of OCV and OPV when coadministered and results are expected in 2017/2018 (Personal Communication, CDC).

M) OCV Use in Special Populations

i. OCV use in HIV-Infected Individuals

Data on how human immunodeficiency virus (HIV) infection influences susceptibility to cholera infection and immune response to OCVs are limited. A study of the 2005 cholera outbreak in Mozambique suggested a higher attack rate among HIV-infected individuals than among non-HIV-infected persons¹⁰². This is important in high HIV-prevalent settings, where cholera remains a persistent occurrence. A case-control study evaluating effectiveness of the WC-rBS vaccine in Mozambique found that the vaccine was 78% protective (95% confidence interval = 39%–92%) in a high HIV prevalence setting (20–30% HIV prevalence)³². An immunogenicity study with Shanchol in Haiti among adults with and without HIV infection showed 74% seroconversion against the Inaba serotype and 65% seroconversion against the Ogawa serotype among HIV positive adults compared with 91% seroconversion against both serotypes in the HIV negative group⁷²; diminished responses were primarily seen among HIV-infected individuals with the lowest CD4 counts. This suggested lower immunogenicity among HIV-infected individuals needs further evaluation with due consideration for the risk of cholera and potential additional dosing regimens among these populations.

ii. OCV use among prison populations

Cholera outbreaks in prisons have long been reported across the world since the 1800s¹⁰³. The source of these outbreaks, which have recorded alarmingly high case fatality rates in some instances, range from infected prisoners exposed within the community who are still shedding when admitted to the prison to contaminated food and water. Prisoners are particularly vulnerable due to overcrowding (some prisons reaching up to 8 times their capacity), poor sanitation and hygiene measures, social marginalization, and inadequate medical services or quarantine actions that favor rapid and prolonged transmission.

Control and prevention measures in use include isolation and quarantine, WASH interventions (installation of hand washing stations, provision of safe water), use of chlorination as a disinfectant, distribution of prophylactic antibiotics, use of emergency treatment units, suspension of visits, and transferring the sick to hospitals/other prisons. However, the ability to implement these measures depends greatly upon available resources, staff, time, and space. Administration of OCVs has rarely been utilized.

Haiti is the first country to have conducted a pre-emptive OCV campaign among prisoners for the prevention of prison outbreaks (Personal Communication, CDC, 2016). Following a national campaign in 2014, the remaining OCV (Shanchol) doses were used to vaccinate prisoners, and staff when possible, in 16 prisons with two doses between November and December of 2014 (11,826 doses dispensed with a total cost of 22,705 USD, not including the vaccine which was borrowed from the global stockpile). Few refused the vaccine and demand was high. A high coverage rate was achieved, which can likely be attributed to the fact that the target population was small and clearly defined. Catch-up vaccinations for those incarcerated following the first dose, and therefore received their first dose during the second dose administration, were left with prison medical staff to be administered 14 days later. Two post-vaccination outbreaks were reported, resulting in only 3 deaths, despite the nationwide increase in cases. In turn, this model showed significant success in involving coordination of many agencies and demonstrated that the OCV use is feasible and potentially a high impact intervention among prison populations.

iii. OCV use in Pregnant Women

Currently the guidance on OCV use in pregnant women is conflicting and ambiguous. The WHO 2010 Position Paper on cholera vaccines mentions pregnant women as a group that, is “especially vulnerable to severe disease and for which the vaccines are not contraindicated” and thus “may also be targeted [for vaccination]”⁵. However, the vaccine package inserts are contradictory, ambiguous and inconsistent. Given that pregnant women are excluded from clinical trials of these vaccines – as is the normal practice with clinical trials of drugs and vaccines – there is lack of data from well-controlled studies on vaccine safety during pregnancy. Consequently, the manufacturers of these vaccines are more cautious.

The package insert for Shanchol states the following – “No specific clinical studies have been performed to evaluate the safety and immunogenicity of Shanchol in pregnant women and for the fetus. The vaccine is therefore not recommended for use in pregnancy. However, Shanchol is a killed vaccine that does not replicate, is given orally and acts locally in the intestine. Therefore, in theory, Shanchol should not pose any risk to the human fetus. Administration of Shanchol to pregnant women may be considered after careful evaluation of the benefits and risks in case of a medical emergency or an epidemic.”

The package insert for Dukoral states the following – “The vaccine may be administered during pregnancy and to lactating women.”

https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=116). However, product information for Dukoral is not always consistent. The Package Leaflet for users cautions that women who are pregnant, think they may be pregnant or are planning to have a baby or are breast-feeding, should ask their doctor before taking the vaccine. In addition, the 26-page Product Monograph produced by Crucell uses language similar to that in the Shanchol™ package insert - “The effect of Dukoral® on embryo-fetal development has not been assessed and animal studies on reproductive toxicity have not been conducted. No specific clinical studies have been performed to address this issue. The vaccine is therefore not recommended for use in pregnancy. However, Dukoral® is an inactivated vaccine that does not replicate. Dukoral® is also given orally and acts locally in the intestine. Therefore, in theory, Dukoral® should not pose any risk to the human fetus. Administration of Dukoral® to pregnant women may be considered after careful evaluation of the benefits and risks.” http://www.crucellvaccinescanada.com/pdf/110808_Dukoral_PM.pdf

Given this ambiguity, immunization program managers have been reluctant to diverge from package insert recommendations most campaigns conducted to date have excluded pregnant women. In 2015, the GTFCC secretariat commissioned a literature review on OCV use in pregnancy, which was reviewed and endorsed by the OCV working group for development of interim guidance while the formal SAGE review process occurred

(http://www.who.int/cholera/vaccines/Risk_Benefits_vaccinating_pregnant_women_Technical_Note_13Jan2016.pdf).

Data on OCV use in pregnancy are limited compared with data on other vaccine characteristics. Two retrospective studies have systematically documented the safety of OCV use in pregnancy – in Zanzibar with Dukoral (2010), in Guinea with Shanchol (2012)^{56,76}, in Malawi¹⁰⁴ and Bangladesh¹⁰⁵. Other studies during OCV campaigns, though not powered to detect effect pregnancy outcomes, have also documented no adverse pregnancy and fetal outcomes among those women who were inadvertently vaccinated¹⁰⁵. A prospective pregnancy outcome study has recently been completed during an OCV campaign in Malawi in 2015. Results support the conclusion that OCVs are safe to be used during pregnancy, and given the risk of poor outcomes from cholera infection in pregnancy, pregnant women should be vaccinated during OCV campaigns¹⁰⁴.

Table 11 lists details of the studies that have evaluated pregnancy related outcomes of OCV use. It is to be noted that randomized trials to evaluate pregnancy outcomes may not be possible given the special need for ethical and moral considerations.

Table 11: List of Studies that have evaluated OCV use in Pregnancy, Until March 2017

Study	Study description	Vaccine used	Birth outcomes	Fetuses exposed to vaccine		Fetuses not exposed to vaccine		Relative risk or odds ratio	P value	Comments
				No.	%	No.	%			
Follow-up surveillance of women who were pregnant during mass reactive vaccination campaign, Guinea, 2012 (Grout L et al. 2014)	Retrospective cohort study involving face-to-face interviews with women in vaccinated area who were pregnant in 2012 during cholera epidemic	Shanchol	Miscarriages (≤ 5 mo. gestation)	n=1,312		n=272		NA	0.689	No significant differences in outcomes found between fetuses exposed and not exposed. Determination of vaccination and fetal outcomes based on interviews with women (plus confirmation via vaccination cards for a minority of those reporting having been vaccinated).
				12	1.4	2	0.7			
				36	2.8	5	1.8		0.394	
Study of birth outcomes following mass cholera vaccination demonstration project, Zanzibar, 2010 (Hashim 2012)	Face-to-face survey of women conducted 9 months after vaccination campaign to identify women pregnant during campaign and birth outcomes among those vaccinated and not vaccinated.	Dukoral	Miscarriages (≤ 20 weeks)	N=196		N=955		Unadjusted RR = 1.45 Adjusted RR = 1.13	0.350	Fetal losses were greater in vaccinated vs. non-vaccinated pregnant women, but differences were not significant and the vaccine group was older, poorer and received less ANC services. Vaccination status determined by vaccination database developed for demonstration project.
				1	0.5	7	0.7			
				9	4.6	20	2.1			
				10	5.1	27	2.8	1.62	0.21	
				3 (out of 186)	1.6	13 (out of 928)	1.4	Adjusted RR = 1.46	0.56	
Safety of a killed oral cholera vaccine (Shanchol) in pregnant women in Malawi: A prospective cohort study (Ali et al., 2016)	The study was conducted in two nearby districts (Nsanje and Chikwawa) in Malawi. Persons ≥ 1 year in Nsanje were offered the vaccine. No vaccinations were administered in Chikwawa. The primary endpoint was pregnancy loss (spontaneous	Shanchol	Total fetal losses	N=835		N=835		Unadjusted RR = 1.28 Adjusted RR = 1.24	0.52	No significant differences in outcomes found between fetuses exposed and not exposed. Relatively paucity of data on possible miscarriage during the first trimester. Miscarriages are more likely to occur in the first trimester
				23	2.75	18	2.16			
				N=679	1.18	N=673	0.89	Unadjusted RR = 1.32	0.60	
	Neonatal death	8		6						

Study	Study description	Vaccine used	Birth outcomes	Fetuses exposed to vaccine		Fetuses not exposed to vaccine		Relative risk or odds ratio	P value	Comments	
				No.	%	No.	%				
	miscarriage or stillbirth, which was compared between women exposed to OCV and women not-exposed to OCV.		Malformation	N=822 2	0.24	N=823 1	0.12	Unadjusted RR = 2.0	0.57	but the enrollment occurred following the vaccine campaign, and miscarriages may have already occurred prior to enrollment; thus, the study was unable to fully characterize the risk of 1st trimester pregnancy loss following OCV vaccination	
Safety of the oral cholera vaccine in pregnancy: Retrospective findings from a subgroup following mass vaccination campaign in Dhaka, Bangladesh (Khan et al.)	Retrospective case control study; following a mass vaccination campaign, of pregnancy women who inadvertently received vaccine. The primary end points included any adverse events, spontaneous abortions, stillbirths, and congenital anomalies.	Shanchol	Any adverse event	N = 69 11	16%	N = 69 8	12%	Unadjusted OR = 1.55	0.38	Percent of adverse event and spontaneous abortions were greater in the vaccinated group, but significant differences in outcomes were found.	
			Spontaneous Abortion	N = 69 5	7%	N = 69 1	1.4%	Unadjusted OR = 5.3			
			Stillbirth	N = 69 6	9%	N = 69 6	9%	Unadjusted OR = 1			There was substantial loss to follow-up in the study that resulted in a small sample size. Women in the vaccinated group were also followed at an earlier stage making then inherently more likely of reporting adverse events.
			Congenital Anomaly	N = 69 0	0%	N = 69 1	1.4%	Unadjusted OR = 0			

3.4. Global Oral Cholera Vaccine Stockpile

A global cholera vaccine stockpile has been in existence since 2013. As part of a comprehensive cholera control strategy, in September 2011, WHO convened an ad hoc experts' meeting where stockpiling OCV was endorsed as an additional, but necessary and feasible response mechanism for cholera control in outbreak and emergency settings. The stockpile was created to facilitate access to OCVs for underserved populations especially in outbreak and emergency settings, while increasing demand and production resulting in lower unit costs and greater equity of distribution. Accordingly, in June 2013, a global OCV stockpile was created with an initial investment of 2 million doses by multiple partners. In November 2013, the Gavi board endorsed funding support for the OCV stockpile with an investment of \$115 million over 5 years (2014 – 2018). The OCV stockpile is managed as a rotating fund by the International Coordinating Group (ICG) which manages similar stockpiles of meningococcal meningitis and yellow fever vaccines for outbreak response. The ICG is comprised of four decision making partners: the International Federation of Red Cross and Red Crescent Societies (IFRC), Médecins Sans Frontières (MSF), United Nations Children's Fund (UNICEF) and WHO, which also serves as the Secretariat. Information on requesting the stockpile vaccine is available at http://www.who.int/cholera/vaccines/ocv_stockpile_2013/en/.

The stockpile was initially established to increase access and availability of OCVs in outbreak and humanitarian emergencies, which remains the primary objective. In addition, discussions within the GTFCC and the different GTFCC working groups highlighted the need to include OCVs within comprehensive cholera prevention and control strategies in recurrent outbreak situations in endemic settings. Since 2015, the OCV working group of the GTFCC proposed that the stockpile be divided into two components – emergency stock and non-emergency reserve (Figure 4). Decisions regarding OCV release from the emergency stockpile are managed by the ICG, and the OCV working group of the GTFCC is responsible for decisions on vaccine release from the non-emergency stock.

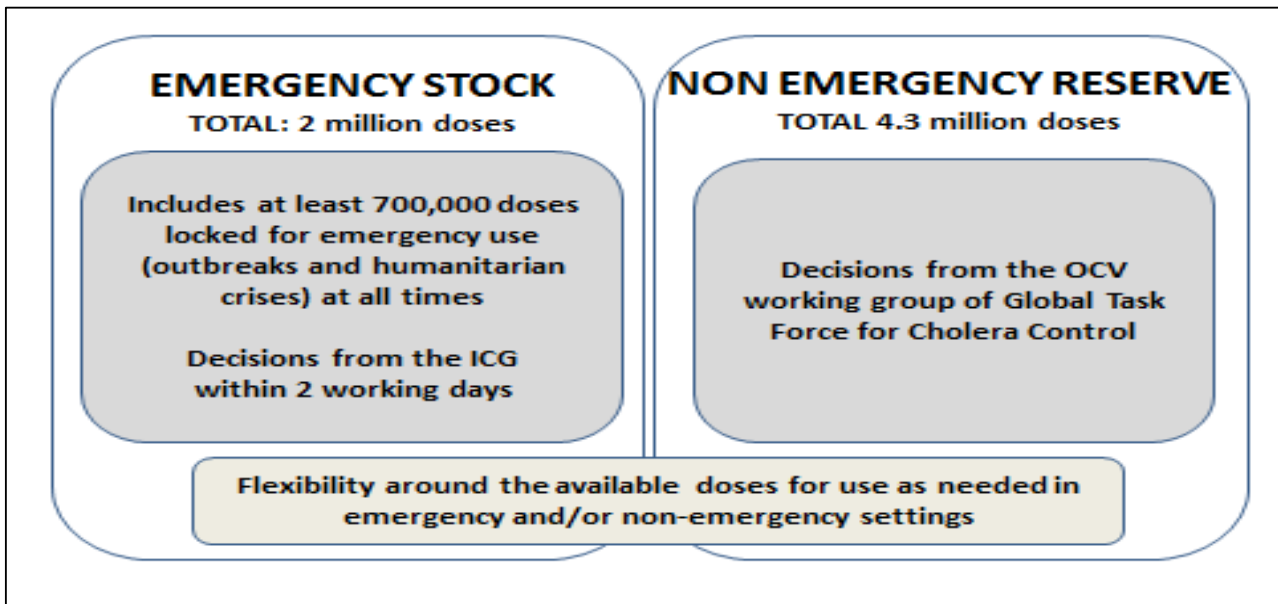
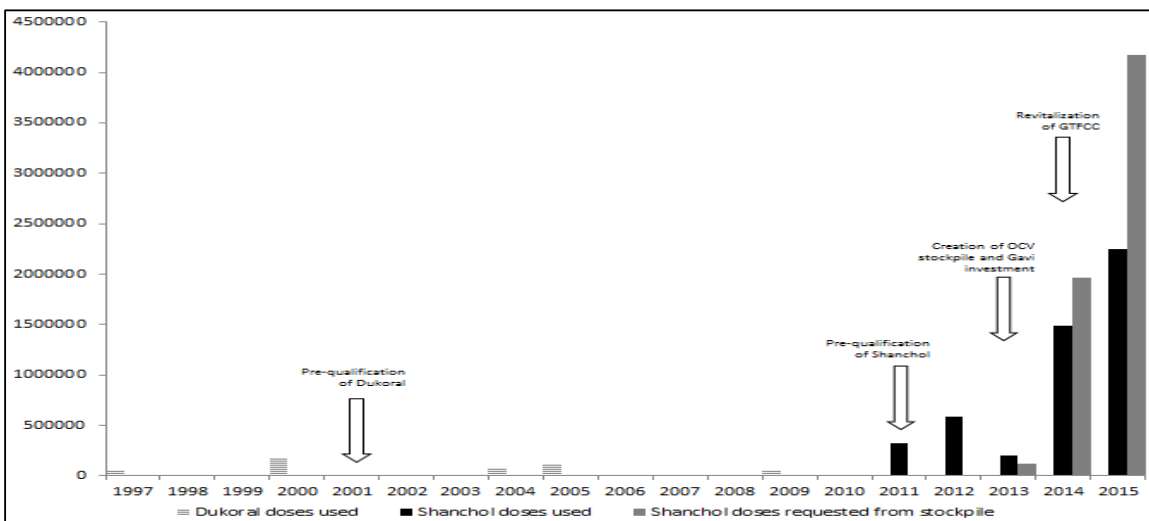


Figure 4: Global OCV Stockpile Components and Number of Available Doses, 2016

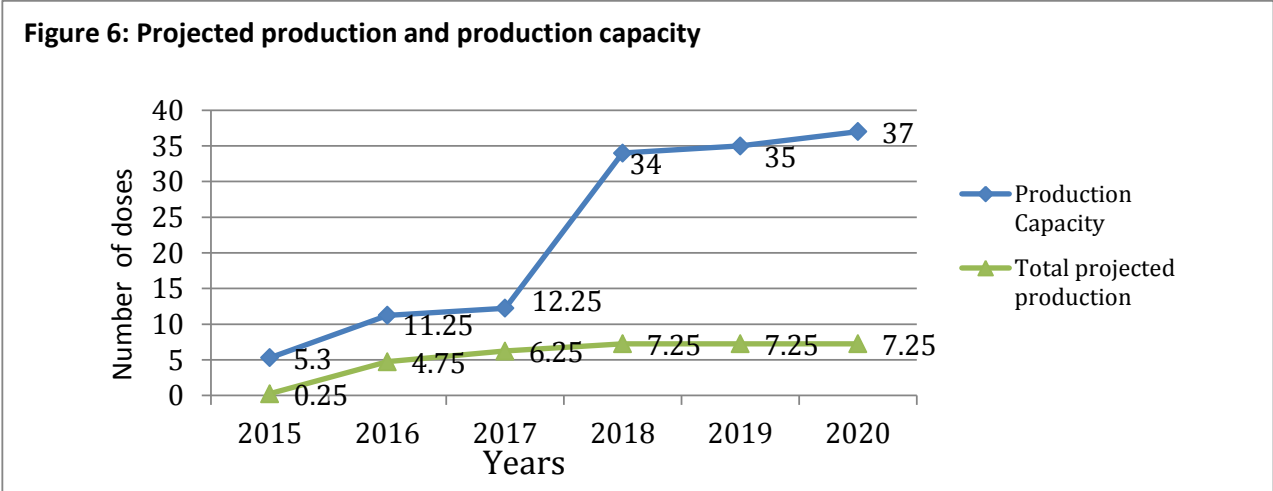
Over 7 million doses have been deployed from the global OCV stockpile with successful use in humanitarian crises, outbreaks, and endemic settings (Figure 5 shows data until 2015 with 5 million doses used). Since the inception of the stockpile, OCV availability and supply, as well as OCV requests have steadily increased. In 2015, OCV demand exceeded available supply highlighting the need for increased production.

Figure 5: Oral cholera vaccine use and demand 1997-2015



In the current investment period for the OCV stockpile, Shanchol production will remain at approximately 2 million doses per year. Current projections for Evuichol production are for 3-4 million

doses per year, with a maximum production capacity of up to 25 million doses per year (Figure 6). The Bangladesh modified WC only OCV could add another 20 – 40 million doses, initially only for the in-country market, but if eventually prequalified, to the international market. Though forecast demand for oral cholera vaccine has increased, the international global health community should remain cautiously optimistic until vaccine production meets projected demand.



While an increased body of evidence is available regarding OCV safety, effectiveness, acceptability and cost-effectiveness, more evidence is needed in other areas, notably impact on disease transmission, vaccine dosing and alternative strategies (including incorporation within routine immunization programs and coadministration with other vaccines, alternative delivery strategies, and controlled temperature chain). Unconventional approaches can serve to improve success and even decrease cost, and alternative vaccination strategies, such as the use of a single dose regimen and extended dosing intervals could offer increased benefit to populations with difficulty accessing the traditional two round campaigns. Oral vaccines against enteric infections, including cholera vaccines, have been less immunogenic and efficacious when given to those living in less developed countries, especially in young children. Though the rationale is not completely understood, key factors associated with poor oral vaccine performance in children in developing countries appear to be related to the intestinal environment of these populations. Specific factors that need to be evaluated further include protein energy and micronutrient malnutrition, maternal antibody interference, concomitant parasitic infections, and intestinal mucosal damage due to environmental enteropathy.

Recently, in June 2016, the Gavi board endorsed support for the operational costs of OCV campaigns (<http://www.gavi.org/about/governance/gavi-board/minutes/2016/22-june/minutes/02e---consent-agenda---oral-cholera-vaccines-operational-cost-support/>). The current Gavi investment for the OCV stockpile covers the period from 2014 – 2018. OCVs will be reconsidered by the Gavi board in 2018 for ongoing long-term support, based on information gathered during the investment period, notably on impact and cost. Hence, monitoring and evaluation, and implementation research is a critical component of OCV use, to help generate the data for appropriately targeting OCV use and maximizing efficient use of OCVs in different contexts and settings.

4. Grading for Recommendations, Assessment, Development and Evaluation (GRADE) Review

4.1. Introduction and Objectives

In accordance to the guidance document for the development of evidence-based vaccine related recommendations (http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf), the SAGE OCV working group, established in late 2015/early 2016 (Appendix 1) held a series of conference calls and face-to-face meetings to decide on the priority questions to be addressed and for which recommendations need to be developed for SAGE consideration. Accordingly the SAGE OCV WG, prioritized a list of issues for good practice recommendations and for the formal Grading of Recommendations, Assessment, Development and Evaluation (GRADE) review.

The following key questions and outcomes were agreed upon by the working group for a formal GRADE review,

1. What is the evidence that the currently available killed, whole-cell oral cholera vaccines (OCVs) are safe among non-pregnant individuals (Dukoral \geq 2 years old, Shanchol/Euvichol/mORCVax \geq 1 year olds?
2. What is the evidence for protective efficacy, effectiveness, and duration of the currently available killed, whole cell OCVs during the first 5 years following immunization among individuals \geq 1 year old?
3. What is the evidence that the currently available killed, whole-cell oral cholera vaccines (OCVs) are safe among pregnant women?

4.2. Methodology

A thorough literature search was conducted using PubMed to identify all relevant articles using the following search terms - oral cholera vaccine, cholera vaccine effectiveness, cholera vaccine impact, cholera vaccine safety and immunogenicity, cholera vaccine acceptance or acceptability, cholera vaccine use, cholera vaccines in pregnancy. The initial search was conducted in the English language and was later expanded to include Spanish, French, and Russian (Courtesy: Epicentre). An additional search was conducted to identify publications associated with OCV use in pregnancy. An attempt was made to reach out to key cholera vaccine researchers for unpublished data.

Given the large number of studies and evaluations related to safety of OCVs, the SAGE OCV working group made a decision to restrict the GRADE review to randomized controlled trials (RCTs) for the safety question, and to use observational studies as corroborating evidence. A decision was made to focus on data available since 2009 when the newer cholera vaccines became available and are now included in the OCV stockpile. For review of efficacy/effectiveness/duration and safety in pregnancy, all studies including RCTs and observational studies were included. Articles were not considered to be mutually exclusive and an article could provide evidence to answer more than one question of interest.

A total of 28 published studies were included in the GRADE review – 10 for vaccine safety, 20 for vaccine efficacy/effectiveness/duration of protection and 4 for safety among pregnant women.

Outcomes of interest for safety included any adverse event, any serious adverse event, and death. Efficacy, effectiveness, and duration outcomes included efficacy/effectiveness against any cholera (among all ages, <5 year olds, 5–14 year olds, and >14 year olds), efficacy/effectiveness against severe cholera (among all ages, <5 year olds, 5–14 year olds, and >14 year olds). duration for at least 6 months, duration for at least 3 years, and for a few studies duration at for at least 5 years. Safety during pregnancy outcomes of interest consisted of any adverse event, miscarriages, stillbirths, small for gestational age, congenital anomalies, preterm birth, low birth weight, and infant/neonatal death. However, no articles that were reviewed captured information on low birth weight, preterm birth and low birth weight.

A summary of the each publication was prepared using a standard template summarizing the study details, including the study setting, methods, results and limitations, and the details were verified by an additional reviewer. All publications were assessed and graded in terms of their risk of bias, level of indirectness, degree of imprecision, strength of association, and degree of residual confounding.

4.3. Results

Detailed results of the evidence and GRADE review and included in Appendix 2, Appendix 3 and Appendix 4. The key results are summarized here.

Question: What is the evidence that the currently available killed, whole-cell oral cholera vaccines (OCVs) are safe among non-pregnant individuals (Dukoral \geq 2 years old, Shanchol/Euvichol/mORCVax \geq 1 year olds)?

Conclusion: High level of scientific evidence that the currently licensed OCVs are safe.

Question: What is the evidence for protective efficacy, effectiveness, and duration of the currently available killed, whole cell OCVs during the first 5 years following immunization among individuals \geq 1 year old?

Conclusion: Moderate level of scientific evidence that the currently licensed oral cholera vaccines are efficacious and effective with duration of at least 6 months for a single dose. Moderate level of evidence that the currently available oral cholera vaccines with a 2-dose schedule are efficacious and effective for at least 3 years among adults, but not among young children 1 – 5 years old. There is low level of evidence that the currently available OCVs are effective for at least 5 years (only 2 studies).

Question: What is the evidence that the currently available killed, whole-cell oral cholera vaccines (OCVs) are safe among pregnant women?

Conclusion: Moderate level of scientific evidence that the currently licensed OCVs are safe for use during pregnancy.

An additional meta-analysis review has been conducted by the OCV working group of the GTFCC and led by Johns Hopkins University. The paper submitted for publication as attached as additional evidence (Appendix 5).

5. Proposed OCV Recommendations for SAGE Consideration

5.1. General Recommendations

1. Given the current availability of prequalified WC, killed, oral cholera vaccines (OCVs) and data on their safety, efficacy, field effectiveness, feasibility, impact and acceptability in cholera-affected populations, these vaccines should be used in areas with endemic cholera, in humanitarian crisis with high risk of cholera and during cholera outbreaks, in conjunction with other cholera prevention and control strategies.
2. Appropriate case management, WaSH interventions, surveillance and community mobilization remain cornerstones of cholera control. Vaccination is synergistic with those activities.
3. The main objective of vaccination is to reduce disease burden in vaccinated areas, through individual and herd protection, and to prevent the spatial expansion of outbreaks.
4. Mass vaccination campaigns are usually the most practical option for delivering oral cholera vaccines. Schools, religious institutions and other community settings can be appropriate venues for vaccination campaigns using fixed sites. Outreach activities can also be organized. Incorporating cholera vaccination with other vaccination activities can be an alternative or complementary strategy to mass campaigns.
5. Cholera vaccination mass campaigns should be accompanied by WaSH interventions and combined with other health-related interventions.
6. Epidemiological and laboratory surveillance is essential to estimate the burden of disease and understand the impact of vaccination and other interventions.
7. Equitable access to OCV should be ensured for underserved populations exposed to the risk of cholera. OCV stockpiles, supported by GAVI and managed by the ICG (for emergency type of use) and by the GTFCC OCV working group (for use in endemic settings), have been formally established in 2013 for that purpose. Requests to access OCV in any setting should follow the established mechanisms of stockpile management.
8. In all settings, a series of criteria should be considered to guide the decision to vaccinate,
 - The risk of cholera among targeted populations
 - The susceptibility and vulnerability of the population and the risk of spatial extension.
 - The capacity to cover as many persons as possible, eligible to receive the vaccine and living in the targeted area (e.g., ages ≥ 1 or 2 years, depending on the vaccine).
 - Programmatic factors such as the local capacity to organize and conduct a campaign, ability to provide other priority health interventions and population acceptability.

- Cholera vaccination should not be conducted if a campaign has been conducted in the previous 3 years in the same population (with consideration for the quality of the campaign, the vaccine coverage, and any population movements)
9. Countries and agencies accessing the OCV stockpiles should systematically implement M&E activities and provide accompanying data to WHO GTFCC. In particular, M&E activities should provide better estimates of,
- The impact of OCV to control and prevent cholera outbreaks, including in humanitarian emergency situations
 - The impact of OCV on cholera transmission in endemic settings
 - The vaccine effectiveness using different vaccination strategies and in different age groups
 - The cost-effectiveness of different vaccination strategies and in various settings and age groups
- Guidelines have been developed for this purpose and are accessible on the WHO website.
10. Based on available evidence, there are considerable benefits and very few risks for including pregnant women in OCV vaccination campaigns.
11. OCV should be considered for emergency/relief workers who are likely to be directly exposed to cholera patients or to contaminated food or water, particularly those staying in areas with poor access to healthcare facilities.
12. Vaccination is generally not recommended for long- or short-term travelers to cholera-affected countries.

5.2. Control of Endemic Cholera

13. Cholera vaccination should be targeted in priority to high-risk areas or groups, regularly affected by cholera; with culture-confirmed cases detected in at least three out of the last five years and evidence of local transmission. Campaign planning should be carried out to ensure that vaccination takes place prior to any known cholera season.
14. Cholera vaccination in endemic areas should be contingent on multisectoral interventions as part of a long-term plan for cholera prevention and control endorsed at the local and national levels by the relevant ministries and should be budgeted for.
15. Universal vaccination (throughout a country without regard to risk) is not recommended in most countries.
16. Follow up campaigns in the same areas may be considered after 3 years in case of persistent transmission.
17. Strategies targeting specific age groups at higher risk may be considered.

5.3. Cholera Control in Humanitarian Emergencies

18. During humanitarian emergencies with a risk of cholera, but without current cholera outbreak, vaccination with OCV should systematically be considered to help prevent potential outbreaks, as an additional preparedness measure, depending on the local infrastructure (i.e., capacity to organize a vaccination campaign).
19. The decision to vaccinate should be guided by a thorough investigation of the current and historical epidemiological situation, an assessment of the actual risk of cholera, and a clear identification of geographical areas and populations to be targeted.
20. Campaign planning should be carried out to ensure that vaccination takes place prior to any known cholera season. Campaign preparation should be conducted early to ensure that vaccination starts immediately once the vaccines become available in country.
21. In areas of protracted emergencies, follow-up campaigns may be considered after 3 years (or less in case of persistent risk, particularly in case of population movement).

5.4. Control of Cholera Outbreaks

22. Cholera vaccination should systematically be considered to help prevent the spread of current outbreaks to new areas, following a thorough investigation of the current and historical epidemiological situation and a clear identification of geographical areas and populations to be targeted.
23. Campaign preparation should be conducted early to ensure that vaccination starts immediately once the vaccines become available in country.
24. Based on available evidence on short-term protection, a single dose strategy could be considered in areas experiencing cholera outbreaks. Considering the limited evidence about the duration of protection, additional vaccination might be needed to ensure longer-term protection.

5.5. Needs for additional research and evaluation

25. Vaccine coverage
 - Conducting coverage surveys focusing on missed vaccination in high-risk groups may provide essential information to improve overall impact and cost-effectiveness of OCV campaigns.
26. Adverse Events Following Immunization (AEFI)
 - As OCVs have been used extensively in multiple settings globally and have been proven to be safe, AEFI monitoring using routine passive surveillance based on country-level policies may be conducted. Active surveillance should be reserved for new delivery strategies or newer generation cholera vaccines as they become available.

27. Economic analysis

- It is important to perform systematic economic analyses to measure intervention cost, cost effectiveness and cost benefit in different settings where campaigns have been conducted.

28. Vaccine efficacy and effectiveness

- Additional research is needed to better inform number of doses, optimal dosing interval (dose spacing) and issues related to duration of protection in different settings. More information is needed on the effectiveness in children 1—5 years old.
- Further assessment of herd protection is needed.

29. Vaccination impact

- There is a need to further work on methodologies to measure the impact of vaccination by better defining relevant and meaningful comparison groups and identify standardized indicators across geographies and settings.

30. Alternative strategies of OCV delivery

- Alternative delivery strategies such as self-administration, outside-the-cold-chain (CTC / ECTC), linking OCV with other health interventions should be further evaluated in a large variety of settings.
- More information is needed on coadministration of OCV with other vaccines, especially with oral vaccines such as OPV and rotavirus vaccine.

6. Other Oral Cholera Vaccines in Development

a) Vaxchora (PaxVax Inc., USA) —Live Attenuated, Single Dose Oral Cholera Vaccine

The live, attenuated single-dose OCV manufactured in the United States called Vaxchora (manufactured by PaxVax has recently been licensed for adult travelers (18–64 years old) to cholera-affected areas who are between the ages of 18–64 years (<http://paxvax.com/about/news/cdc-advisory-committee-immunization-practices-votes-recommend-vaxchora-paxvax%E2%80%99s-single>). Vaxchora received marketing approval from the United States (U.S.) Food and Drug Administration (FDA) on June 10, 2016. Vaxchora was redeveloped from a previously available vaccine (Orochol/Mutachol) which was licensed in several countries¹⁰⁶ but manufacturing was discontinued as a result of corporate mergers.

Vaxchora protects against toxigenic strains of *Vibrio cholera* O1 but not against serogroups O139. It presents as a double-chambered aluminum foil sachet containing the vaccine strain CVD103-HgR. A cold chain (2–8°C) is required. No major safety issues have been detected. The most common adverse reactions were tiredness, headache, abdominal pain, nausea/vomiting, lack of appetite and diarrhea. Efficacy, based on challenge studies for the vaccine has been demonstrated to be approximately 60–90% with a duration of approximately 3 months¹⁰⁷. Vaxchora is the only live single-dose vaccine for cholera currently licensed.

Additional information on Vaxchora is available at - <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2016-06/cholera-02-wong.pdf> and elsewhere¹⁰⁸.

b) Hillchol (Hilleman Laboratories, India) — Modified killed whole cell vaccine with cholera toxin B subunit

A new killed OCV is under development by researchers at University of Goteborg and Hilleman Laboratories, India. The simplified production approach focuses on using one genetically engineered cholera El Tor Hikojima strain that undergoes a single inactivation method. Inclusion of a recombinant low cost cholera toxin with the B subunit in the new formulation would avoid the need for buffer co-administration, strict cold chain requirements, and would offer short term cross protection against enterotoxigenic (ETEC) diarrhea. This modified WC-rBS candidate has been shown to be immunogenic in mice. If shown to be safe and protective in humans, this option could result in lower manufacturing costs and substantially reduce OCV prices. Future work on a new oral mucosal adjuvant for a second generation version may further potentiate intestinal immune responses, leading to improved long term protection among all age groups.

c) Vibrio cholera 638 (Finlay Institute, Cuba) — live attenuated single dose cholera vaccine

A potential live attenuated candidate, *Vibrio cholerae* 638 is under development by researchers at the Finley Institute in Cuba. Researchers are currently attempting to simplify the production process by decreasing the number of strains and using a single inactivation mechanism in order to ultimately reduce the price. The vaccine candidate uses the *vibrio cholera* O1 El Tor Ogawa strain to formulate a single oral dose with the attempt to remove the virulence factor (CT) through CTXPhu and hapA deletion. This vaccine is within the Phase 2 and Phase 3 of development. The formulation, buffer, cold chain requirements, safety, efficacy, and duration are yet to be determined.

d) VA 1.3 and VA1.4 (India) — live attenuated single dose cholera vaccine

The Indian government is currently developing a live attenuated OCV, VA1.3 and VA1.4, that is in Phase 2 of the development process. The vaccine candidate uses the *vibrio cholera* O1 El Tor Ogawa (non-toxigenic) strain to formulate a single, oral dose. VA1.4 cholera vaccine is identical to VA1.3 except for absence of Ampicillin marker. The vaccine attempts to remove the main virulence factor through ctxB gene introduction using a series of genetic manipulations. Formulation, buffer, cold chain requirements, safety, efficacy, and duration are yet to be determined.

e) CholeraGarde (China) — live attenuated single dose cholera vaccine

Designed as a single dose candidate, the live attenuated oral cholera vaccine called CholeraGarde, is under development in China using the *vibrio cholera* O1 El Tor biotype and Inaba serotype. In attempt to remove the main virulence factor, researchers are working to genetically modify the strain through VCT and recA deletion. Formulation, buffer, cold chain requirements, safety, efficacy, and duration are yet to be determined. Phase 2 studies are ongoing to determine safety and immunogenicity.

f) OraVAX – currently commercialized, supplied through China and the Philippines

The currently commercialized vaccine, OraVax, uses the *vibrio cholera* O1 strain. The 3 dose enteric-coated capsule regimen does not require a buffer and is recommended for children (>10 years old) and adults. The main differences with Dukoral include no requirement for rBS (no buffer), the inclusion of 5 instead of 4 cholera strains, and potentially pricing.

Similar to Euvichol, non-inferiority evaluations with Shanchol are underway for another formulation of the whole cell, killed OCV - Cholvax (Incepta, Bangladesh). Once complete, the aim is to increase production capacity, enabling vaccination of large populations at risk in Bangladesh.

Table 12 lists the characteristics of the newer cholera vaccines and vaccine candidates.

Table 12: Key characteristics and features of other OCVs

Name	Vaxchora	Hillchol	Vibrio Cholerae 638	VA 1.3, 1.4	CholeraGarde	OraVAX
Target	Travelers ages 18-64 years	TBD	TBD	TBD	TBD	≥11 yo
Regimen	Single dose	Single dose	Single dose	Single dose	Single dose	3 doses (0, 7, and 28 days)
Duration of protection	~3 months	TBD	TBD	TBD	TBD	TBD
Age range for vaccination	18-64 years old	TBD	TBD	TBD	TBD	≥11 years old
Requirement for oral buffer	1 sachet of buffer	TBD	TBD	TBD	TBD	Buffer not required
Storage temperature	2-8°C	TBD	TBD	TBD	TBD	2-8°C
Shelf life	TBD	TBD	TBD	TBD	TBD	TBD
WHO Prequalification status	TBD	TBD	TBD	TBD	TBD	TBD
Price to the public sector (per dose)	TBD	TBD	TBD	TBD	TBD	~10\$
Comments	Supplier country: US	Supplier country: India	Supplier country: Cuba	Supplier country: India	Supplier Country: China	Supplier country: China, Philippines

7. References

1. Ali M, Lopez AL, You YA, et al. The global burden of cholera. *Bull World Health Organ* 2012; **90**(3): 209-18a.
2. Cholera, 2015. *Releve epidemiologique hebdomadaire / Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record / Health Section of the Secretariat of the League of Nations* 2016; **91**(38): 433-40.
3. Clemens JD, Nair GB, Ahmed T, Qadri F, Holmgren J. Cholera. *Lancet* 2017.
4. Lindenbaum J, Greenough WB, Islam MR. Antibiotic therapy of cholera. *Bull World Health Organ* 1967; **36**(6): 871-83.
5. Cholera vaccines: who position paper. *Weekly Epidemiological Record* 2010; **85**(13): 117-28.
6. WHO consultation on oral cholera vaccine (OCV) stockpile strategic framework: potential objectives and possible policy options, Geneva, Switzerland, 18-20 September 2011. WHO consultation on oral cholera vaccine (OCV) stockpile strategic framework: potential objectives and possible policy options, Geneva, Switzerland, 18-20 September 2011; 2012 :27 pp 3 ref. Geneva: World Health Organization.
7. Tauxe RV. Cholera. In: Evans AS, Brachman PS, eds. *Bacterial Infections of Humans: Epidemiology and Control*. Boston, MA: Springer US; 1998: 223-42.
8. Cholera, 2014. *Releve epidemiologique hebdomadaire / Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record / Health Section of the Secretariat of the League of Nations* 2015; **90**(40): 517-28.
9. Kaper JB, Morris JG, Jr., Levine MM. Cholera. *Clinical microbiology reviews* 1995; **8**(1): 48-86.
10. Siddique AK, Nair GB, Alam M, et al. El Tor cholera with severe disease: a new threat to Asia and beyond. *Epidemiology and Infection* 2009; **138**(3): 347-52.
11. Chowdhury F, Kuchta A, Khan AI, et al. The increased severity in patients presenting to hospital with diarrhea in Dhaka, Bangladesh since the emergence of the hybrid strain of *Vibrio cholerae* O1 is not unique to cholera patients. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* 2015; **40**: 9-14.
12. Nair GB, Qadri F, Holmgren J, et al. Cholera due to altered El Tor strains of *Vibrio cholerae* O1 in Bangladesh. *J Clin Microbiol* 2006; **44**(11): 4211-3.
13. Jackson BR, Talkington DF, Pruckler JM, et al. Seroepidemiologic survey of epidemic cholera in Haiti to assess spectrum of illness and risk factors for severe disease. *Am J Trop Med Hyg* 2013; **89**(4): 654-64.
14. Merrell DS, Butler SM, Qadri F, et al. Host-induced epidemic spread of the cholera bacterium. *Nature* 2002; **417**(6889): 642-5.
15. Cholera, 2010. *Releve epidemiologique hebdomadaire / Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record / Health Section of the Secretariat of the League of Nations* 2011; **86**(31): 325-39.

16. Cholera, 2011. *Releve epidemiologique hebdomadaire / Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record / Health Section of the Secretariat of the League of Nations* 2012; **87**(31/32): 289-304.
17. Cholera, 2012. *Releve epidemiologique hebdomadaire / Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record / Health Section of the Secretariat of the League of Nations* 2013; **88**(31): 321-34.
18. Cholera, 2013. *Releve epidemiologique hebdomadaire / Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record / Health Section of the Secretariat of the League of Nations* 2014; **89**(31): 345-55.
19. Alajo SO, Nakavuma J, Erume J. Cholera in endemic districts in Uganda during El Nino rains: 2002-2003. *African health sciences* 2006; **6**(2): 93-7.
20. Martinez PP, Reiner RC, Jr., Cash BA, et al. Cholera forecast for Dhaka, Bangladesh, with the 2015-2016 El Nino: Lessons learned. *PLoS One* 2017; **12**(3): e0172355.
21. Martinez-Urtaza J, Huapaya B, Gavilan RG, et al. Emergence of Asiatic Vibrio diseases in South America in phase with El Nino. *Epidemiology (Cambridge, Mass)* 2008; **19**(6): 829-37.
22. Ohtomo K, Kobayashi N, Sumi A, Ohtomo N. Relationship of cholera incidence to El Nino and solar activity elucidated by time-series analysis. *Epidemiol Infect* 2010; **138**(1): 99-107.
23. Ali M, Nelson AR, Lopez AL, Sack DA. Updated global burden of cholera in endemic countries. *PLoS Negl Trop Dis* 2015; **9**(6): e0003832.
24. Group WHOAHCWV. Background Paper on the Integration of Oral Cholera Vaccines into Global Cholera Control Programmes, 2009.
25. Ontweka LN, Deng LO, Rauzier J, et al. Cholera Rapid Test with Enrichment Step Has Diagnostic Performance Equivalent to Culture. *PLoS One* 2016; **11**(12): e0168257.
26. Organization. WH. The Treatment of diarrhoea : a manual for physicians and other senior health workers. Geneva, Switzerland, 2005.
27. Organization WH. Cholera Outbreak: Assessing the Outbreak Response and Improving Preparedness. Geneva: WHO, 2004.
28. Organization WH. Cholera Prevention and Control: Comprehensive and Multidisciplinary Approaches to Tackle an Ancient Disease, 2012.
29. Clemens JD, Sack DA, Harris JR, et al. Cross-protection by B subunit-whole cell cholera vaccine against diarrhea associated with heat-labile toxin-producing enterotoxigenic Escherichia coli: results of a large-scale field trial. *Journal of Infectious Diseases* 1988; **158**(2): 372-7.
30. Clemens JD, Sack DA, Harris JR, et al. Field trial of oral cholera vaccines in Bangladesh: results from three-year follow-up. *Lancet* 1990; **335**(8684): 270-3.
31. Cavaller P, Lucas M, Perroud V, et al. Feasibility of a mass vaccination campaign using a two-dose oral cholera vaccine in an urban cholera-endemic setting in Mozambique. *Vaccine* 2006; **24**(22): 4890-5.

32. Lucas ME, Deen JL, von Seidlein L, et al. Effectiveness of mass oral cholera vaccination in Beira, Mozambique. *New England Journal of Medicine* 2005; **352**(8): 757-67.
33. Trach DD, Clemens JD, Ke NT, et al. Field trial of a locally produced, killed, oral cholera vaccine in Vietnam. *Lancet* 1997; **349**(9047): 231-5.
34. Anh DD, Canh DG, Lopez AL, et al. Safety and immunogenicity of a reformulated Vietnamese bivalent killed, whole-cell, oral cholera vaccine in adults. *Vaccine* 2007; **25**(6): 1149-55.
35. Desai SN, Akalu Z, Teshome S, et al. A Randomized, Placebo-Controlled Trial Evaluating Safety and Immunogenicity of the Killed, Bivalent, Whole-Cell Oral Cholera Vaccine in Ethiopia. *American Journal of Tropical Medicine & Hygiene* 2015; **93**(3): 527-33.
36. Desai SN, Akalu Z, Teshome S, et al. A randomized, double-blind, controlled trial to evaluate the safety and immunogenicity of killed oral cholera vaccine (Shanchol) in healthy individuals in Ethiopia. *International journal of infectious diseases*, 2014. <http://onlinelibrary.wiley.com/doi/10.1016/j.ijid.2014.09.037> (accessed).
37. Desai SN, Akalu Z, Teferi M, et al. Comparison of immune responses to a killed bivalent whole cell oral cholera vaccine between endemic and less endemic settings. *Tropical Medicine & International Health* 2016; **21**(2): 194-201.
38. Sur D, Kanungo S, Sah B, et al. Efficacy of a low-cost, inactivated whole-cell oral cholera vaccine: results from 3 years of follow-up of a randomized, controlled trial. *PLoS Neglected Tropical Diseases [electronic resource]* 2011; **5**(10): e1289.
39. Bhattacharya SK, Dipika S, Ali M, et al. 5 year efficacy of a bivalent killed whole-cell oral cholera vaccine in Kolkata, India: a cluster-randomised, double-blind, placebo-controlled trial. *Lancet Infectious Diseases* 2013; **13**(12): 1050-6.
40. Qadri F, Ali M, Chowdhury F, et al. Feasibility and effectiveness of oral cholera vaccine in an urban endemic setting in Bangladesh: a cluster randomised open-label trial. *Lancet* 2015; **386**(10001): 1362-71.
41. Kanungo S, Paisley A, Lopez AL, et al. Immune responses following one and two doses of the reformulated, bivalent, killed, whole-cell, oral cholera vaccine among adults and children in Kolkata, India: a randomized, placebo-controlled trial. *Vaccine* 2009; **27**(49): 6887-93.
42. Kanungo S, Desai SN, Nandy RK, et al. Flexibility of oral cholera vaccine dosing-a randomized controlled trial measuring immune responses following alternative vaccination schedules in a cholera hyper-endemic zone. *PLoS Neglected Tropical Diseases [electronic resource]* 2015; **9**(3): e0003574.
43. Qadri F, Wierzba TF, Ali M, et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *New England Journal of Medicine* 2016; **374**(18): 1723-32.
44. Charles RC, Hilaire IJ, Mayo-Smith LM, et al. Immunogenicity of a killed bivalent (O1 and O139) whole cell oral cholera vaccine, Shanchol, in Haiti. *PLoS Neglected Tropical Diseases [electronic resource]* 2014; **8**(5): e2828.
45. Baik YO, Choi SK, Olveda RM, et al. A randomized, non-inferiority trial comparing two bivalent killed, whole cell, oral cholera vaccines (Euvichol vs Shanchol) in the Philippines. *Vaccine* 2015; **33**(46): 6360-5.

46. Martin S, Lopez AL, Bellos A, et al. Post-licensure deployment of oral cholera vaccines: a systematic review. *Bulletin of the World Health Organization* 2014; **92**(12): 881-93.
47. Legros D, Paquet C, Perea W, et al. Mass vaccination with a two-dose oral cholera vaccine in a refugee camp. *Bulletin of the World Health Organization* 1999; **77**(10): 837-42.
48. Dorlencourt F, Legros D, Paquet C, Neira M, Ivanoff B, Saout EI. Effectiveness of mass vaccination with WC/rBS cholera vaccine during an epidemic in Adjumani district, Uganda. *Bulletin of the World Health Organization* 1999; **77**(11): 949-50.
49. Jeuland M, Lucas M, Clemens J, Whittington D. A cost-benefit analysis of cholera vaccination programs in Beira, Mozambique. *World Bank Economic Review* 2009; **23**(2): 235-67.
50. Jeuland M, Cook J, Poulos C, Clemens J, Whittington D, Group DCEs. Cost-effectiveness of new-generation oral cholera vaccines: a multisite analysis. *Value in Health* 2009; **12**(6): 899-908.
51. Chaignat CL, Monti V, Soepardi J, et al. Cholera in disasters: do vaccines prompt new hopes? *Expert Review of Vaccines* 2008; **7**(4): 431-5.
52. Schaetti C, Weiss MG, Ali SM, et al. Costs of illness due to cholera, costs of immunization and cost-effectiveness of an oral cholera mass vaccination campaign in Zanzibar. *PLoS Neglected Tropical Diseases [electronic resource]* 2012; **6**(10): e1844.
53. Schaetti C, Ali SM, Hutubessy R, Khatib AM, Chaignat CL, Weiss MG. Social and cultural determinants of oral cholera vaccine uptake in Zanzibar. *Human vaccines & Immunotherapeutics* 2012; **8**(9): 1223-9.
54. Schaetti C, Ali SM, Chaignat CL, Khatib AM, Hutubessy R, Weiss MG. Improving community coverage of oral cholera mass vaccination campaigns: lessons learned in Zanzibar. *PLoS ONE [Electronic Resource]* 2012; **7**(7): e41527.
55. Khatib AM, Ali M, von Seidlein L, et al. Effectiveness of an oral cholera vaccine in Zanzibar: findings from a mass vaccination campaign and observational cohort study. *The Lancet Infectious Diseases* 2012; **12**(11): 837-44.
56. Hashim R, Khatib AM, Enwere G, et al. Safety of the recombinant cholera toxin B subunit, killed whole-cell (rBS-WC) oral cholera vaccine in pregnancy. *PLoS Neglected Tropical Diseases [electronic resource]* 2012; **6**(7): e1743.
57. Schaetti C, Chaignat CL, Hutubessy R, et al. Social and cultural determinants of anticipated acceptance of an oral cholera vaccine prior to a mass vaccination campaign in Zanzibar. *Human Vaccines* 2011; **7**(12): 1299-308.
58. Schaetti C, Hutubessy R, Ali SM, et al. Oral cholera vaccine use in Zanzibar: socioeconomic and behavioural features affecting demand and acceptance. *BMC Public Health* 2009; **9**: 99.
59. Anh DD, Lopez AL, Tran HT, et al. Oral cholera vaccine development and use in Vietnam. *PLoS Medicine / Public Library of Science* 2014; **11**(9): e1001712.
60. Thiem VD, Deen JL, von Seidlein L, et al. Long-term effectiveness against cholera of oral killed whole-cell vaccine produced in Vietnam. *Vaccine* 2006; **24**(20): 4297-303.
61. Vu DT, Hossain MM, Nguyen DS, et al. Coverage and costs of mass immunization of an oral cholera vaccine in Vietnam. *Journal of Health, Population & Nutrition* 2003; **21**(4): 304-8.

62. Sur D, Lopez AL, Kanungo S, et al. Efficacy and safety of a modified killed-whole-cell oral cholera vaccine in India: an interim analysis of a cluster-randomised, double-blind, placebo-controlled trial. [Erratum appears in Lancet. 2010 Oct 23;376(9750):1392]. *Lancet* 2009; **374**(9702): 1694-702.
63. Wierzba TF, Kar SK, Mogasale VV, et al. Effectiveness of an oral cholera vaccine campaign to prevent clinically-significant cholera in Odisha State, India. *Vaccine* 2015; **33**(21): 2463-9.
64. Mogasale V, Kar SK, Kim JH, et al. An Estimation of Private Household Costs to Receive Free Oral Cholera Vaccine in Odisha, India. *PLoS Neglected Tropical Diseases [electronic resource]* 2015; **9**(9): e0004072.
65. Kar SK, Sah B, Patnaik B, et al. Mass vaccination with a new, less expensive oral cholera vaccine using public health infrastructure in India: the Odisha model. *PLoS Neglected Tropical Diseases [electronic resource]* 2014; **8**(2): e2629.
66. Kar SK, Pach A, Sah B, et al. Uptake during an oral cholera vaccine pilot demonstration program, Odisha, India. *Human vaccines & Immunotherapeutics* 2014; **10**(10): 2834-42.
67. Uddin MJ, Wahed T, Saha NC, et al. Coverage and acceptability of cholera vaccine among high-risk population of urban Dhaka, Bangladesh. *Vaccine* 2014; **32**(43): 5690-5.
68. Khan IA, Saha A, Chowdhury F, et al. Coverage and cost of a large oral cholera vaccination program in a high-risk cholera endemic urban population in Dhaka, Bangladesh. *Vaccine* 2013; **31**(51): 6058-64.
69. Rouzier V, Severe K, Juste MA, et al. Cholera vaccination in urban Haiti. *American Journal of Tropical Medicine & Hygiene* 2013; **89**(4): 671-81.
70. Severe K, Rouzier V, Anglade SB, et al. Effectiveness of Oral Cholera Vaccine in Haiti: 37-Month Follow-Up. *American Journal of Tropical Medicine & Hygiene* 2016; **94**(5): 1136-42.
71. Ivers LC, Hilaire IJ, Teng JE, et al. Effectiveness of reactive oral cholera vaccination in rural Haiti: a case-control study and bias-indicator analysis. *The Lancet Global Health* 2015; **3**(3): e162-8.
72. Ivers LC, Charles RC, Hilaire IJ, et al. Immunogenicity of the Bivalent Oral Cholera Vaccine Shanchol in Haitian Adults With HIV Infection. *Journal of Infectious Diseases* 2015; **212**(5): 779-83.
73. Ivers LC, Teng JE, Lascher J, et al. Use of oral cholera vaccine in Haiti: a rural demonstration project. *American Journal of Tropical Medicine & Hygiene* 2013; **89**(4): 617-24.
74. Aibana O, Franke M, Teng J, Hilaire J, Raymond M, Ivers LC. Cholera vaccination campaign contributes to improved knowledge regarding cholera and improved practice relevant to waterborne disease in rural Haiti. *PLoS Neglected Tropical Diseases* 2013; **7**(11).
75. Burnett E, Dalipanda T, Ogaoga D, et al. Knowledge, Attitudes, and Practices regarding Diarrhea and Cholera following an Oral Cholera Vaccination Campaign in the Solomon Islands. *PLoS Negl Trop Dis* 2016; **10**(8): e0004937.
76. Grout L, Martinez-Pino I, Ciglencecki I, et al. Pregnancy Outcomes after a Mass Vaccination Campaign with an Oral Cholera Vaccine in Guinea: A Retrospective Cohort Study. *PLoS Neglected Tropical Diseases [electronic resource]* 2015; **9**(12): e0004274.
77. Luquero FJ, Grout L, Ciglencecki I, et al. Use of *Vibrio cholerae* vaccine in an outbreak in Guinea. *New England Journal of Medicine* 2014; **370**(22): 2111-20.

78. Luquero FJ, Grout L, Ciglenecki I, et al. First outbreak response using an oral cholera vaccine in Africa: vaccine coverage, acceptability and surveillance of adverse events, Guinea, 2012. *PLoS Neglected Tropical Diseases [electronic resource]* 2013; **7**(10): e2465.
79. Ciglenecki I, Sakoba K, Luquero FJ, et al. Feasibility of mass vaccination campaign with oral cholera vaccines in response to an outbreak in Guinea. *PLoS Medicine / Public Library of Science* 2013; **10**(9): e1001512.
80. Phares CR, Date K, Travers P, et al. Mass vaccination with a two-dose oral cholera vaccine in a long-standing refugee camp, Thailand. *Vaccine* 2016; **34**(1): 128-33.
81. Tohme RA, Francois J, Wannemuehler K, et al. Oral Cholera Vaccine Coverage, Barriers to Vaccination, and Adverse Events following Vaccination, Haiti, 2013(1). *Emerging Infectious Diseases* 2015; **21**(6): 984-91.
82. Peprah D, Palmer JJ, Rubin GJ, et al. Perceptions of oral cholera vaccine and reasons for full, partial and non-acceptance during a humanitarian crisis in South Sudan. *Vaccine* 2016; **34**(33): 3823-7.
83. Azman AS, Rumunu J, Abubakar A, et al. Population-Level Effect of Cholera Vaccine on Displaced Populations, South Sudan, 2014. *Emerging Infectious Diseases* 2016; **22**(6): 1067-70.
84. Abubakar A, Azman AS, Rumunu J, et al. The First Use of the Global Oral Cholera Vaccine Emergency Stockpile: Lessons from South Sudan. *PLoS Medicine / Public Library of Science* 2015; **12**(11): e1001901.
85. Msyamboza KP, M'Bang'ombe M, Hausi H, et al. Feasibility and acceptability of oral cholera vaccine mass vaccination campaign in response to an outbreak and floods in Malawi. *The Pan African medical journal* 2016; **23**: 203.
86. Lam E, Al-Tamimi W, Russell SP, et al. Oral Cholera Vaccine Coverage during an Outbreak and Humanitarian Crisis, Iraq, 2015. *Emerg Infect Dis* 2017; **23**(1): 38-45.
87. Clemens J, Shin S, Ali M. New approaches to the assessment of vaccine herd protection in clinical trials. *Lancet Infect Dis* 2011; **11**(6): 482-7.
88. Ali M, Emch M, von Seidlein L, et al. Herd immunity conferred by killed oral cholera vaccines in Bangladesh: a reanalysis. *Lancet* 2005; **366**(9479): 44-9.
89. Ali M, Sur D, You YA, et al. Herd protection by a bivalent killed whole-cell oral cholera vaccine in the slums of Kolkata, India. *Clinical Infectious Diseases* 2013; **56**(8): 1123-31.
90. Kanungo S, Desai SN, Saha J, et al. An Open Label Non-inferiority Trial Assessing Vibriocidal Response of a Killed Bivalent Oral Cholera Vaccine Regimen following a Five Year Interval in Kolkata, India. *PLoS Neglected Tropical Diseases [electronic resource]* 2015; **9**(5): e0003809.
91. Jeuland M, Whittington D. Cost-benefit comparisons of investments in improved water supply and cholera vaccination programs. *Vaccine* 2009; **27**(23): 3109-20.
92. Kim SY, Choi Y, Mason PR, Rusakaniko S, Goldie SJ. Potential impact of reactive vaccination in controlling cholera outbreaks: an exploratory analysis using a Zimbabwean experience. *South African Medical Journal Suid-Afrikaanse Tydskrif Vir Geneeskunde* 2011; **101**(9): 659-64.
93. Azman AS, Luquero FJ, Ciglenecki I, Grais RF, Sack DA, Lessler J. The Impact of a One-Dose versus Two-Dose Oral Cholera Vaccine Regimen in Outbreak Settings: A Modeling Study.[Erratum appears in PLoS Med. 2016 Mar;13(3):e1001989; PMID: 26966905]. *PLoS Medicine / Public Library of Science* 2015; **12**(8): e1001867.

94. Dimitrov DT, Troeger C, Halloran ME, Longini IM, Chao DL. Comparative effectiveness of different strategies of oral cholera vaccination in Bangladesh: a modeling study. *PLoS Neglected Tropical Diseases [electronic resource]* 2014; **8**(12): e3343.
95. Reyburn R, Deen JL, Grais RF, et al. The case for reactive mass oral cholera vaccinations. *PLoS Neglected Tropical Diseases [electronic resource]* 2011; **5**(1): e952.
96. Azman AS, Lessler J. Reactive vaccination in the presence of disease hotspots. *Proceedings of the Royal Society of London - Series B: Biological Sciences* 2015; **282**(1798): 20141341.
97. Ali M, Emch M, Yunus M, Clemens J. Modeling spatial heterogeneity of disease risk and evaluation of the impact of vaccination. *Vaccine* 2009; **27**(28): 3724-9.
98. Saha A, Khan A, Salma U, et al. The oral cholera vaccine Shanchol™ when stored at elevated temperatures maintains the safety and immunogenicity profile in Bangladeshi participants. *Vaccine* 2016; **34**(13): 1551-8.
99. Emperador DM, Velasquez DE, Estivariz CF, et al. Interference of Monovalent, Bivalent, and Trivalent Oral Poliovirus Vaccines on Monovalent Rotavirus Vaccine Immunogenicity in Rural Bangladesh. *Clin Infect Dis* 2016; **62**(2): 150-6.
100. Polio vaccines: WHO position paper - March, 2016. *Releve epidemiologique hebdomadaire / Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record / Health Section of the Secretariat of the League of Nations* 2016; **91**(12): 145-68.
101. Kollaritsch H, Que JU, Kunz C, Wiedermann G, Herzog C, Cryz SJ, Jr. Safety and immunogenicity of live oral cholera and typhoid vaccines administered alone or in combination with antimalarial drugs, oral polio vaccine, or yellow fever vaccine. *J Infect Dis* 1997; **175**(4): 871-5.
102. von Seidlein L, Wang XY, Macumule A, et al. Is HIV infection associated with an increased risk for cholera? Findings from a case-control study in Mozambique. *Tropical medicine & international health : TM & IH* 2008; **13**(5): 683-8.
103. Poulet J. [The 1832 cholera epidemic in the prisons of Paris]. *La semaine des hopitaux : organe fonde par l'Association d'enseignement medical des hopitaux de Paris* 1973; **49**(41): 2717-22.
104. Ali M, Nelson A, Luquero FJ, et al. Safety of a killed oral cholera vaccine (Shanchol) in pregnant women in Malawi: an observational cohort study. *Lancet Infect Dis* 2017.
105. Khan AI, Ali M, Chowdhury F, et al. Safety of the oral cholera vaccine in pregnancy: Retrospective findings from a subgroup following mass vaccination campaign in Dhaka, Bangladesh. *Vaccine* 2017; **35**(11): 1538-43.
106. Ryan ET, Calderwood SB, Qadri F. Live attenuated oral cholera vaccines. *Expert Rev Vaccines* 2006; **5**(4): 483-94.
107. Chen WH, Cohen MB, Kirkpatrick BD, et al. Single-dose Live Oral Cholera Vaccine CVD 103-HgR Protects Against Human Experimental Infection With *Vibrio cholerae* O1 El Tor. *Clin Infect Dis* 2016; **62**(11): 1329-35.
108. Levine MM, Chen WH, Kaper JB, Lock M, Danzig L, Gurwith M. PaxVax CVD 103-HgR single-dose live oral cholera vaccine. *Expert Rev Vaccines* 2017; **16**(3): 197-213.

UPDATE WITH THE DEVELOPMENT OF EBOLA VACCINES AND IMPLICATIONS TO INFORM FUTURE POLICY RECOMMENDATIONS

1 | POLICY QUESTIONS AND OVERALL CONCLUSIONS

1. Are there remaining challenges that may prevent access to Ebola vaccines in future outbreaks, and, if yes, can SAGE make recommendations on how these might be addressed?

- A dozen candidate vaccines (including monovalent, bivalent or multivalent candidates) underwent or are actively undergoing clinical development at different trial phases. Seven vaccines have completed or are in trials up to Phase I stage, 4 vaccines up to or in Phase II stage, and one vaccine has completed Phase III stage. The Phase III trial for an rVSV-vectored candidate vaccine (rVSVΔG-ZEBOV-GP) was undertaken in Guinea and is the only study that demonstrates clinical efficacy and effectiveness for any candidate Ebola vaccine.
- In addition, another prime/boost candidate vaccine based on rVSV- and Ad5-vectored components (GamEvac-Combi) is licensed in its country of origin. However, the full dossier has not been yet made available to the WHO Secretariat for review.
- The rVSVΔG-ZEBOV-GP candidate vaccine with efficacy data was granted access to the Priority Medicine (PRIME) scheme by the European Medicine Agency and Breakthrough Therapy designation by the US Food and Drug Administration.
- To date, no vaccine has been WHO-prequalified or completed the WHO Emergency Use Assessment and Listing (EUAL) procedure. The rVSVΔG-ZEBOV-GP candidate vaccine and a prime/boost candidate vaccine based on Ad26- and MVA-vectored components (Ad26.ZEBOV/MVA-BN-Filo) have submitted EUAL documentation to the WHO Secretariat. For both vaccines, submissions were accepted and evaluated on a rolling basis and the formal EUAL review by an ad-hoc Committee for the Emergency Use of Vaccines is planned for the second or third quarter of 2017.
- Potentially, various licensure pathways exist for candidate vaccines. Developers are consulting individually with regulatory agencies to define the documentation and evidence that is needed. Requirements and procedures are thus being discussed one by one.
- The WHO Secretariat is implementing the work plan of the R&D Blueprint for Action to Prevent Epidemics, including experts' deliberations on future clinical trials for candidate Ebola vaccines. The WG recommended that there should be alignment of different initiatives (e.g. Coalition for Epidemic Preparedness Innovations [CEPI], and others) to support the development and licensure

THIS SUMMARY INCLUDES

1 | Policy questions and overall conclusions 1

2 | Key findings 3

- Epidemiology 3

- Vaccine development 3

- Vaccine approval..... 6

- Modelling of vaccination strategies 7

- Emergency and post-licensure access 11

3 | Recommendations proposed by SAGE Working Group ... 12

4 | Bibliography 14

5 | Appendices..... 15

- Outbreak characteristics..... 15

- Vaccine clinical trials..... 18

THIS SUMMARY DOES NOT INCLUDE

The full extent of the evidence reviewed by the SAGE Working Group is not included.

of Ebola vaccines and of other vaccines against epidemic-prone diseases, taking note of the mandates specific to each stakeholder.

2. Is the current evidence sufficient for SAGE to make recommendations regarding the use of Ebola vaccines in case of another Ebola outbreak (pre-licensure and/or post licensure)? If yes, which recommendations can be proposed? If not, what key data are missing?

- A single dose of rVSVΔG-ZEBOV-GP has shown 100% efficacy (95% confidence interval: 64–100%) in a cluster randomised ring vaccination trial conducted in Guinea. Ring vaccination with the same candidate vaccine was also carried out following the smaller flare-ups in 2016 in Guinea, Sierra Leone and Liberia.
- The duration of the immune responses elicited by the Ebola vaccines under development is currently documented for the observed follow-up periods of the trials. These periods remain short. As of March 2017, the longest interval for which such data is available is 12 months (published and unpublished data on the prime/boost Ad26/MVA, rVSVΔG-ZEBOV-GP, and ChAd3-EBOZ vaccines). Although the understanding of the immune response to both natural infection and vaccination remains incomplete, it is expected that prime/boost vaccines offer better prospects of long-term protection to an Ebola virus infection than a single dose schedule. However, vaccines that elicit an earlier immune response after a single/first dose are likely to be more useful during outbreaks.
- Another uncertainty is whether vaccines protecting against *Zaire Ebola virus* species afford cross-protection against other species of Ebola virus and other filoviruses. At least five vaccines under development are also being tested clinically in bivalent or multivalent formulations that may protect against other species of Ebola virus or Marburg virus.
- Because no candidate Ebola vaccine has received regulatory approval for use to date, discussions are ongoing jointly with 13 African Member States to guarantee Expanded Access (compassionate use, while safeguarding ethical and good clinical practice precautions) to rVSVΔG-ZEBOV-GP in the event of an outbreak. Evidence from Phase I–III clinical trials and from the deployments during the 2016 flare-ups as well as modelling results comparing different vaccination strategies justify Expanded Access this candidate vaccine in a ring vaccination modality in outbreak responses. In addition to logistical arrangements, the preparation includes consultation and formal review of a protocol for an open-label, non-randomized, single arm study with the governments, national regulatory agencies and national ethics committees of the concerned 13 African countries.
- In the event of an outbreak in the near future, doses of rVSVΔG-ZEBOV-GP may be available from different sources. Researchers in West Africa have a few thousand doses left from the trials, currently stored under Good Clinical Practices conditions. The manufacturer reported that there are a few thousand doses in stock that are owned by the US Biomedical Advanced Research and Development Authority. In addition, the manufacturer is producing 300,000 doses that have been purchased by GAVI Alliance.

2 | KEY FINDINGS

Epidemiology

From 1976 to March 2017, 25 filoviruses outbreaks with ≥ 4 reported human cases have been documented (see, **Appendix 1**). *Zaire ebolavirus* caused 13 of these outbreaks (30,101 reported cases in total), *Sudan ebolavirus* six (777), *Bundibugyo ebolavirus* two (185), and *Marburg marburgvirus* four (425). When the 2013–2016 West African epidemic is omitted, the range of reported cases for the 12 remaining *Zaire ebolavirus* outbreaks was 11–318 (median=64.5). **Figure 1** illustrates the epidemic curve of such an outbreak.(1) The 2013–2016 *Zaire ebolavirus* epidemic in West Africa was unprecedented in its geographical spread and total number of reported cases, but this epidemic lasted slightly longer than a Marburg virus outbreak that began in October 1998 in Angola (109 vs. 100 weeks).(2, 3) When these two occurrences are omitted, the outbreaks have lasted between 1 and 42 weeks, with a median duration of 10 weeks. Other filoviruses known to infect humans are *Reston ebolavirus* (asymptomatic infections only in persons exposed to non-human primates and pigs from the Philippines) and *Tai Forest ebolavirus* (single case of a scientist who did an autopsy on a wild chimpanzee in Ivory Coast).(4, 5)

Since the 1995 Kikwit outbreak, the **principles for interrupting transmission of Ebola and Marburg viruses** are well characterized.(6) These four principles are:

1. infection control in health care facilities and protection of health care workers;
2. detection, management and isolation of patients;
3. surveillance (inclusive of back- and forward contact tracing) and fever surveillance with rapid diagnosis and isolation;
4. community understanding with safe patient and body transport systems, safe burial and household/environmental decontamination.

While these principles were probably not implemented with sufficient rigor and in the proper order initially in the 2013–2016 epidemics of West Africa, they eventually led to transmission interruption.

In the 2013–2016 epidemics of West Africa, reported incidence in children and adolescents was lower than in adults (**Figure 2**) and **health care workers were initially at increased risk** (**Figure 3**). As already observed in previous outbreaks, health care workers can play a role in amplifying an early, low-level transmission of Ebola viruses.

Although already postulated earlier, the 2013–2016 West African epidemic also showed the possibility of **late transmission via semen of Ebola virus disease survivors** as well as transmission via breast milk from a sub-symptomatic mother to her baby.(7-11)

Vaccine development

A dozen candidate vaccines (including monovalent, bivalent or multivalent candidates) underwent or are actively undergoing **clinical development at different trial phases** (**Table 1**). Seven vaccines have completed or are in trials up to Phase I stage, four vaccines up to or in Phase II stage, and one vaccine has completed Phase III stage. **Appendix 2** summarizes the published information on the clinical trials of all these vaccines or their combinations. Some vaccines are tested as single-dose regimen (Ad5-EBOV, ChAd3-EBOZ, rVSVΔG-ZEBOV-GP), while others include a priming and either homologous or heterologous boosting. When prime/boost regimens are tested, the interval between doses is at least 3–4 weeks.

Figure 1. Epidemic curve of Ebola virus disease cases, by transmission mode—Yambuku, Democratic Republic of Congo, 1976 (1)

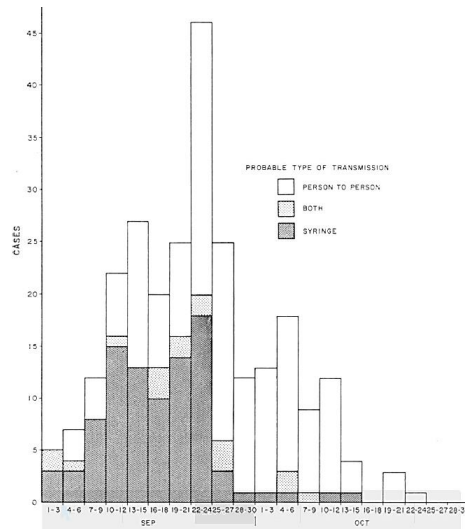


Figure 2. Age-specific cumulative incidence of confirmed and probable Ebola virus disease cases, by country—West Africa, 2013–2016 (12)

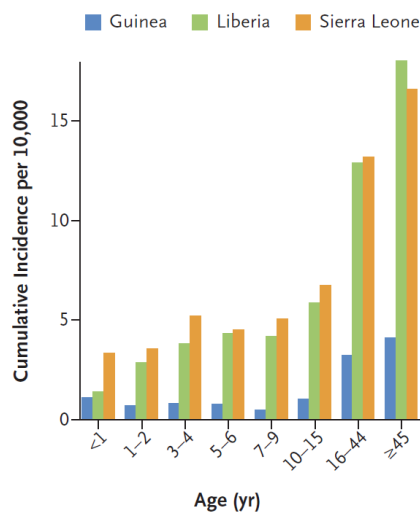


Figure 3. Epidemic curve of Ebola virus disease cases, by health care workers (HCW) and general population—DRC, 1995, and Sierra Leone 2014–2015 (13, 14)

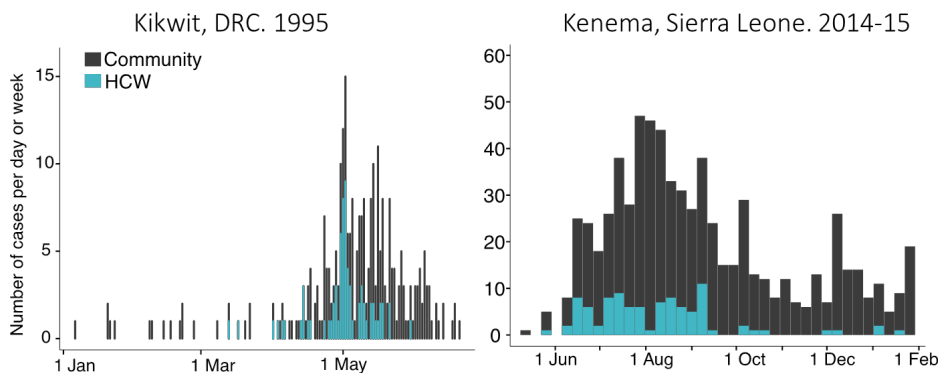
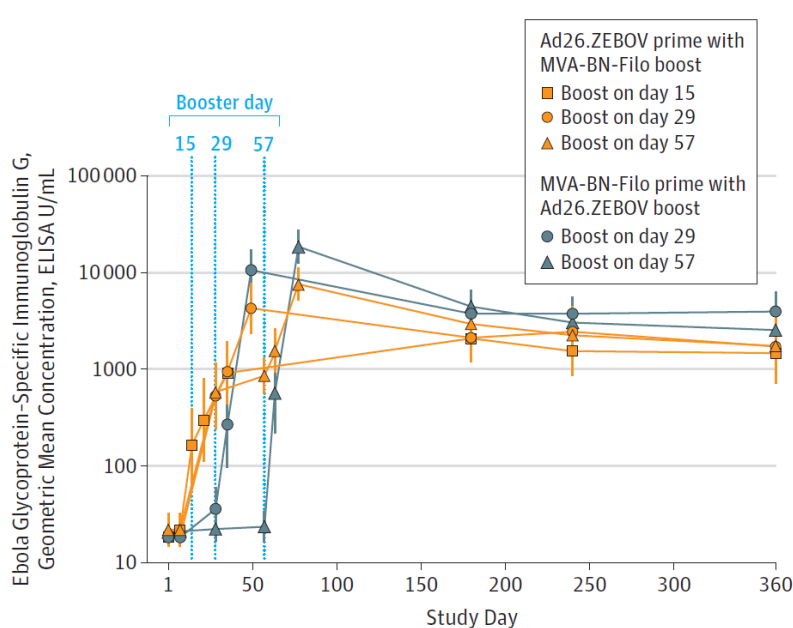


Table 1. Description of candidate Ebola vaccines under clinical development

Candidate vaccine (manufacturer/developer)	Short description of vaccine	Clinical stages
Ad5-EBOV (monovalent) (CanSino Biologics & Beijing Institute of Biotechnology, China)	Non-replicative, recombinant human adenovirus serotype 5 expressing envelope GP of Zaire (Makona strain) Ebola virus species	1 & 2
Ad5 (bivalent) (National Institute of Allergy and Infectious Diseases, USA)	Non-replicative, recombinant human adenovirus serotype 5 expressing envelope GP of Zaire and Sudan Ebola virus species	1 (inactive)
Ad26.ZEBOV & MVA-BN-Filo (prime/boost, VAC52150) (Janssen Vaccines & Prevention B.V, The Netherlands)	Non-replicative, recombinant adenovirus serotype 26 expressing envelope GP of Zaire Ebola virus species and modified vaccinia Ankara expressing 4 filoviruses nucleoproteins (GP for Zaire Ebola [Mayinga strain], Sudan Ebola, and Marburg viruses and nucleoprotein of Tai Forest Ebola virus)	1; currently recruiting for phase 2/3 trials.
ChAd3-EBOZ (monovalent) (GlaxoSmithKline, Belgium)	Non-replicative, recombinant chimpanzee adenovirus serotype 3 expressing envelope GP of Zaire (Mayinga strain) Ebola virus species	1/2a
ChAd3-EBOZ & MVA-BN-Filo (prime/boost) (University of Oxford, UK and National Institute of Allergy and Infectious Diseases, USA)	See previous descriptions	1
ChAd3 (bivalent) (National Institute of Allergy and Infectious Diseases, USA)	Non-replicative, recombinant chimpanzee adenovirus serotype 3 expressing envelope GP of Sudan and Zaire (Mayinga strain) Ebola virus species	1
DNA plasmid vaccines (National Institute of Allergy and Infectious Diseases, USA)	Several candidate vaccines that either encoded both Zaire and Sudan Ebola virus species GP or Marburg virus. <i>Trials carried out in 2004–2010 and none is currently active under NIAID.</i>	1 (inactive)
GamEvac-Combi (rVSV & Ad5, prime/boost) (Gamaleya Research Institute for Epidemiology and Microbiology, Russia)	Replicative, recombinant vesicular stomatitis virus and human adenovirus serotype 5 expressing envelope GP of Zaire (Makona strain) Ebola virus (prime & heterologous boost). <i>MOH of Russian Federation registered vaccine on 28/12/2016 (no. LP-003390).</i>	1/2, 4
rVSVΔG-ZEBOV-GP (Merck, USA)	Replicative, recombinant vesicular stomatitis virus expressing envelope GP of Zaire (Mayinga strain) Ebola virus species with or without homologous boost	1–3
rVSV N4CT1 EBOVGP1 (Profectus BioSciences, USA)	Replicative, recombinant vesicular stomatitis virus expressing GP of Zaire (Mayinga strain) Ebola virus species. (Trivalent Ebola/Zaire, Ebola/Sudan and Marburg candidate vaccine is also been developed.)	1
Nanoparticle recombinant Ebola GP vaccine (Novavax, USA)	Nanoparticle recombinant vaccine with and without our Matrix-M adjuvant; Zaire (Makona strain) Ebola virus species	1
DNA vaccine (INO-4212) (Inovio Pharmaceuticals, USA)	INO-4212 (with 2 components INO-4201 [past Ebola Zaire virus outbreak strains] & INO-4202 [2014–2015 Ebola Zaire virus outbreak strains]), delivered with electroporation	1
HPIV3-EbovZ GP (National Institute of Allergy and Infectious Diseases, USA)	Live-attenuated human parainfluenza virus type 3 vectored expressing Zaire Ebola virus GP. <i>Trial is completed.</i>	1 (inactive)

Data on safety and immunogenicity are accumulating for all candidate vaccines under active clinical development (see, **Appendix 2**). Trials have not reported serious adverse events definitely linked to any candidate vaccine. However, **safety profile** are still been characterized and additional safety information is being generated for children and special populations. Limited systematic head-to-head comparisons are available. All vaccines show detectable humoral and cellular **immune responses** when measured after both priming and boosting (for instance, **Figure 4**). However, follow-up times over which maintenance of these immune responses are documented remain limited. As of March 2017, the longest available interval is 12 months, which refers to the Ad26/MVA vaccine (published data from a Phase I conducted in the UK) and ChAd3-EBOV and rVSVΔG-ZEBOV-GP (unpublished data from a Phase II trials conducted in Liberia).(15) Surrogates of protection are not defined yet.

Figure 4. Humoral immune response to Ad26/MVA vaccine in a Phase I trial (15)



Efficacy and effectiveness data are only available for rVSVΔG-ZEBOV-GP.(16) In a Phase III trial mainly carried out in Guinea in 2015, this vaccine showed a 100% efficacy (95% confidence interval: 64–100%). **Table 2** details the efficacy and effectiveness results from this trial.

Vaccine approval

To date, no vaccine has been WHO-prequalified or completed the WHO Emergency Use Assessment and Listing (EUAL) procedure. The rVSVΔG-ZEBOV-GP candidate vaccine and a prime/boost candidate vaccine based on Ad26- and MVA-vectored components (Ad26.ZEBOV/MVA-BN-Filo) have submitted EUAL documentation to the WHO Secretariat. For both vaccines, submissions were accepted and evaluated on a rolling basis and the formal EUAL review by an ad-hoc Committee for the Emergency Use of Vaccines is planned for the second or third quarter of 2017.

Table 2. Effect of rVSVΔG-ZEBOV-GP on cases of Ebola virus disease in different study populations—Guinea and Sierra Leone (16)

	All clusters*				Randomised clusters†			
	1	2	3	4	5	6	7	8
	All vaccinated in immediate (group A) vs all contacts and contacts of contacts in delayed plus all never-vaccinated in immediate or non-randomised (group B)	All vaccinated in immediate (group A) vs all eligible in delayed plus all eligible never-vaccinated in immediate (group B)	All contacts and contacts of contacts in immediate (group A) vs delayed (group B)	All vaccinated in immediate (group A) vs all eligible never vaccinated in immediate (group B)	All vaccinated in immediate (group A) vs all eligible and consented on day 0 visit in delayed (group B)	All vaccinated in immediate (group A) vs all eligible in delayed (group B)	All eligible in immediate (group A) vs all eligible delayed (group B)	All contacts and contacts of contacts in immediate (group A) vs all contacts and contacts of contacts in delayed (group B)
Group A								
Number of individuals (clusters)	3775 (70)	3775 (70)	7241 (70)	3775 (70)	2108 (51)	2108 (51)	3212 (51)	4513 (51)
Cases of Ebola virus disease (clusters affected)	0 (0)	0 (0)	12 (7)	0 (0)	0 (0)	0 (0)	7 (4)	10 (5)
Attack rate	0%	0%	0.17%	0%	0%	0%	0.22%	0.22%
Group B								
Number of individuals (clusters)	7995 (116)	4507 (104)	4529 (47)	1432 (57)	1429 (46)	3075 (47)	3075 (47)	4529 (47)
Cases of Ebola virus disease (clusters affected)	34 (15)	23 (11)	22 (8)	7 (4)	10 (4)	16 (7)	16 (7)	22 (8)
Attack rate	0.43%	0.51%	0.49%	0.49%	0.7%	0.52%	0.52%	0.49%
Vaccine effect								
Vaccine efficacy/ effectiveness‡ (%; 95% CI)	100% (77.0 to 100.0)	100% (79.3 to 100.0)	70.1% (-4.9 to 91.5)	100% (-51.5 to 100.0)	100% (63.5 to 100.0)	100% (68.9 to 100.0)	64.6% (-46.5 to 91.4)	64.6% (-44.2 to 91.3)
p value§	0.0012	0.0033	0.2759	0.125	0.0471	0.0045	0.344	0.3761

With regard to regulatory agencies, a vaccine (GamEvac-Combi) is licensed in the Russian Federation, its country of origin. Also, rVSVΔG-ZEBOV-GP was granted access to the Priority Medicine (PRIME) scheme by the European Medicine Agency and Breakthrough Therapy designation by the US Food and Drug Administration. Potentially, various licensure pathways exist for candidate vaccines. Developers are consulting individually with regulatory agencies to define the documentation and evidence that is needed.

Modelling of vaccination strategies

The following pre-emptive and reactive vaccination strategies were modelled to assess and compare their impact in controlling Ebola outbreaks:

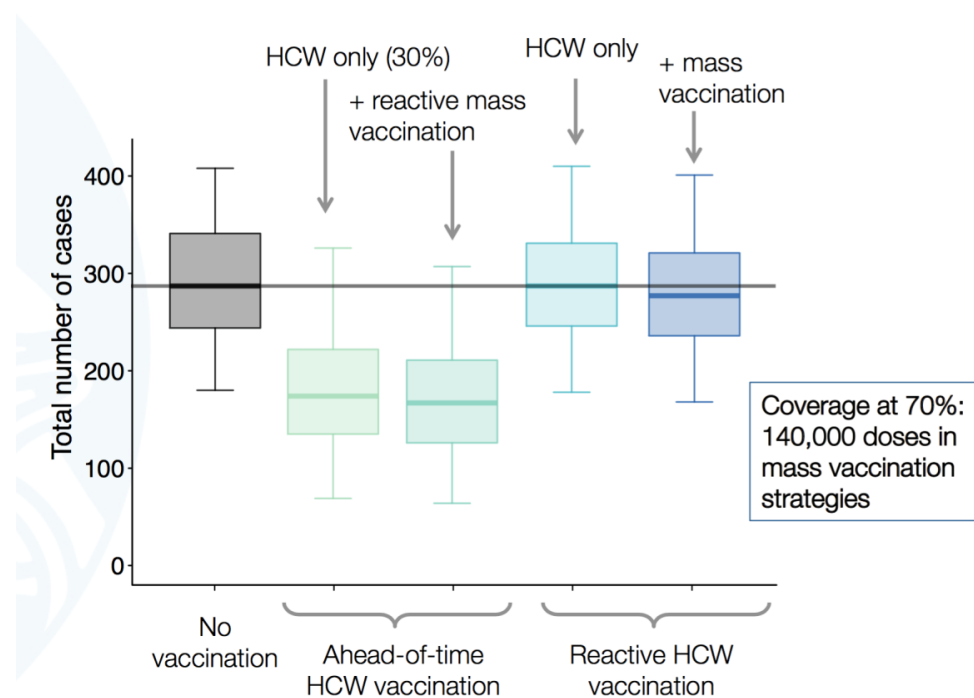
1. **Pre-emptive vaccination** of health-care workers (HCW). Front-line workers (FLW) are not included in HCW because they are recruited after an outbreak is declared.
2. **Reactive vaccination**
 - a) Ring vaccination: contacts and contacts of contacts (CCC) of Ebola virus diseases cases;
 - b) Targeted vaccination: HCW and/or FLW; and
 - c) Mass vaccination: all people living in villages of Ebola virus disease cases plus random allocation of remaining doses in neighbouring areas.

The strategies were assessed on both **localised outbreaks** similar to historical Ebola outbreaks (less than 300 cases and 6 months duration) as well as **widespread outbreaks**, similar to the 2013–16 West African outbreak (30,000 cases and 2 year duration).

Figure 5 shows that pre-emptive vaccination of HCW, even at 30% coverage, can lead to a reduction around 40% of the total number of cases in a scenario similar to the one of Kikwit in 1995, where

HCW played an important role in amplifying the early spread of Ebola virus (see also **Figure 3**). By contrast, reactive vaccination targeting HCW and/or mass-vaccination (70% coverage, 140,000 doses) has a negligible impact due to inherent implementation delays and the rapid control of the outbreak through classical control measures.

Figure 5. Impact of different vaccination strategies on the 1995 Ebola outbreak in Kikwit (Democratic republic of Congo), while accounting for classical control measures implemented during the outbreak



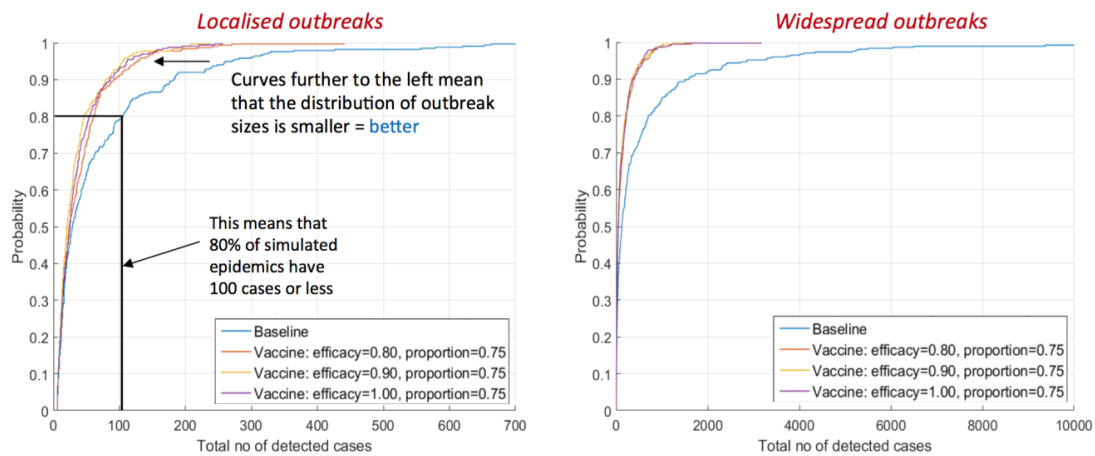
Notes: Each boxplot represents the distribution of the total number of cases expected for a given vaccination strategy, in comparison to the baseline scenario without vaccination (but with classical control measures). Variability arises from multiple stochastic simulations.

Source: Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, presented to the SAGE Working Group on 15 March 2017.

On the other hand, **Figure 6** shows that ring vaccination of CCC is an effective reactive strategy for preventing large outbreaks (>300 cases) when used in conjunction with classical control measures. For instance, in a scenario of localised outbreaks (up to 670 cases), ring vaccination led to a reduction of the probability of observing a large outbreak from 4% to 1%. In a scenario of widespread transmission (up to 10,000 cases), the probability dropped from 33% to 12%, with 95% of the outbreaks having less than 600 cases.

Figure 7 and **Figure 8** compare the impact of different combinations of pre-emptive and reactive strategies for both single-dose and prime/boost vaccines in either rural or urban areas and for different intensity of transmission (as measured by the basic reproduction number R_0). This model is gauged to a baseline with poor or zero initial infrastructures for classical control measures.

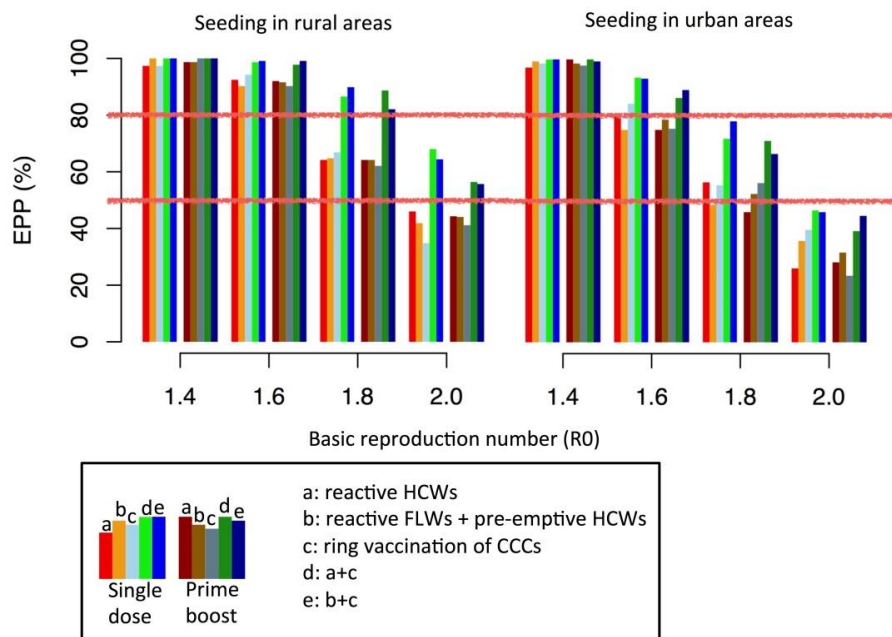
Figure 6. Cumulative probability distribution of the total number of cases with and without ring vaccination and for localised (left panel) and widespread (right panel) outbreaks



Note: Classical control measures are also implemented in this model.

Source: Centre for Outbreak Analysis and Modelling, Imperial College London, presented to the SAGE Working Group on 15 March 2017.

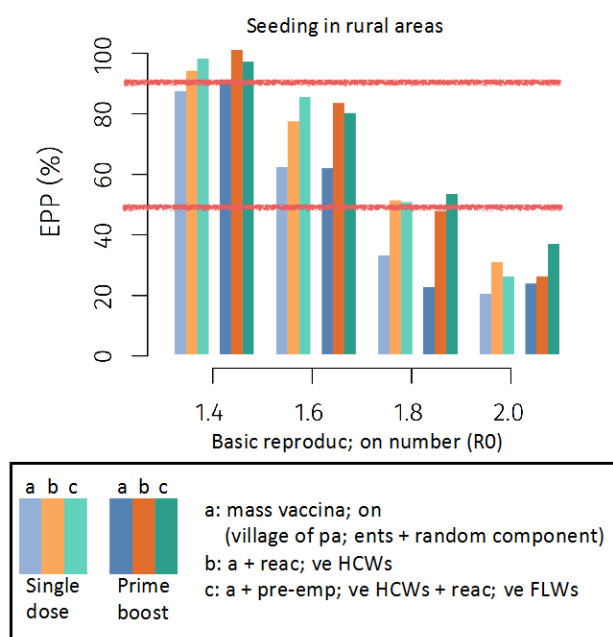
Figure 7. Comparison of the epidemic prevention potential (EPP) for different vaccination strategies, urban vs. rural areas, single dose vs. prime/boost and for different R0 values



Note: EPP is defined as the reduction of the risk of observing a large outbreaks (>300 cases).

Source: Center for Inference & Dynamics of Infectious Diseases, presented to the SAGE Working Group on 15 March 2017.

Figure 8. Comparison of the epidemic prevention potential (EPP) from a rural seeding, for different mass vaccination strategies, single dose vs prime/boost and for different R0 values



Note: EPP is defined as the reduction of the risk of observing a large outbreaks (>300 cases).

Source: Center for Inference & Dynamics of Infectious Diseases, presented to the SAGE Working Group on 15 March 2017.

Taken together, the modelling estimates shows that combining a pre-emptive and/or reactive vaccination of HCW/FLW with ring vaccination of CCC is the most effective strategy as it reduces by more than 80% the risk of large outbreaks (>300 cases) when the epidemic is seeded in rural areas and R0 values are consistent with the 2013–2016 West African outbreak ($R_0 < 2$). Replacing ring vaccination by mass vaccination is less efficient as it reduces the chances of preventing large outbreaks (e.g. from 80% to 50% for $R_0 = 1.8$, see **Figure 8**). This is because ring vaccination targets people at high risk of infection that mass vaccination might miss. It also appears that reducing the risk of large outbreaks is more difficult in urban than in rural areas, due to increased connectivity. Finally, both single-dose and prime/boost (with boosting 28 days after priming) regimens with a similar vaccine efficacy of 90% lead to similar reduction of the risk of large outbreaks.

Although the number of doses needed for pre-emptive vaccination of HCW depends on the health-system of each country, modelling can provide estimates of the number of doses required for the reactive vaccination strategies. Using a ring vaccination strategy, 10,000 doses were sufficient to contain simulated localised outbreaks, whereas 50,000 doses were sufficient to contain simulated widespread outbreaks. By contrast, mass vaccination required a tenfold number of doses.

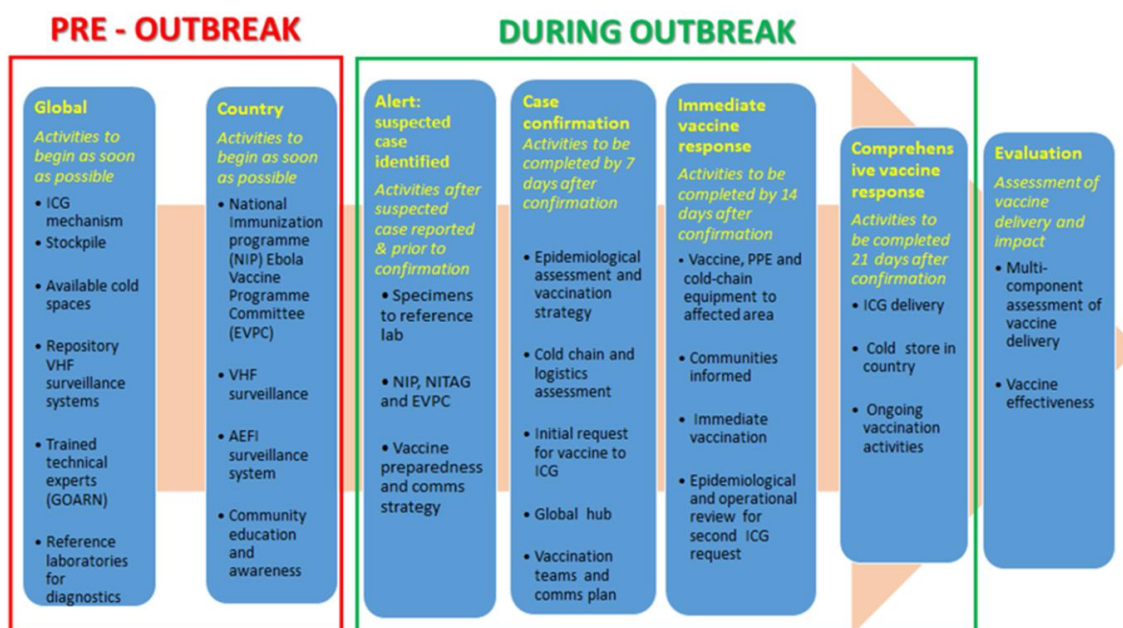
Overall, modelling suggests that pre-emptive vaccination of HCW combined with a reactive ring vaccination strategy is the most effective strategy to contain future Ebola outbreaks. Modelling estimates also support a vaccine stockpile of at least 100,000 doses for reactive ring vaccination. Importantly, ring vaccination requires effective case detection and contact tracing, thus acting synergistically with classical control measure of Ebola virus transmission.

Emergency and post-licensure access

Because no candidate Ebola vaccine has received regulatory approval for use to date, discussions are ongoing jointly with 13 African Member States to guarantee **Expanded Access** (compassionate use, while safeguarding ethical and good clinical practice precautions) to rVSVΔG-ZEBOV-GP in the event of an outbreak. In addition to logistical arrangements, the preparation includes consultation and formal review of a protocol for an open-label, non-randomized, single arm study with the governments, national regulatory agencies and national ethics committees of the concerned 13 African countries. The primary study objective is to measure the incidence of laboratory-confirmed EVD cases 84-days after vaccination; the secondary study objectives are to assess serious adverse events over 84 days after vaccination, adverse events over 28 days after vaccination, and pregnancy outcome. Immunization is by ring vaccination of contacts and of contacts of those contacts around a confirmed case. Only persons who consented after information and who are eligible are vaccinated.

For post-licensure access, the **Global Ebola Vaccine Implementation Team (GEVIT)** has submitted into public consultation a practical guidance on the use of Ebola vaccines in an outbreak response. Its objectives are to improve understanding of the technical specificities of Ebola vaccines and the possible strategies for outbreak response vaccination and to guide global partners and countries on preparedness plans to facilitate rapid vaccination response activities in the event of a future Ebola outbreak. The guide outlines phases that cover both preparation and implementation (**Figure 9**).

Figure 9. Outline of Ebola vaccination phases proposed by the Global Ebola Vaccine Implementation Team



The GAVI Alliance and the manufacturer of the rVSVΔG-ZEBOV-GP candidate vaccine have entered an agreement to support the provision of a vaccine to protect against future Ebola outbreaks. Reserves of rVSVΔG-ZEBOV-GP are available with researchers and the manufacturer.

4 | RECOMMENDATIONS PROPOSED BY SAGE WORKING GROUP

1. Are there remaining challenges that may prevent access to Ebola vaccines in future outbreaks, and, if yes, can SAGE make recommendations on how these might be addressed?

- SAGE notes and appreciates the momentous progress made in the development and evaluation of several vaccine platforms against Ebola and other filoviruses. SAGE wishes to recognize the invaluable contribution of the volunteers who participated in clinical trials, governmental institutions, researchers and their teams, research institutions, regulators and vaccine manufacturers from around the world.
- SAGE urges the WHO Secretariat and national regulatory authorities to intensify their efforts in reaching a consensus and clarity on specific aspects of regulatory pathways that would allow the development and registration of candidate Ebola vaccines, noting the changing Ebola epidemiology and the anticipated constraints in documenting clinical efficacy and effectiveness data. In particular, SAGE supports the role that the WHO Secretariat is playing in facilitating regulatory convergence through development of WHO Guidelines for Ebola vaccines evaluation that will be considered by the Expert Committee on Biological Standardization. Regulatory convergence on data requirements and wider understanding of various regulatory pathways such as the Animal Efficacy Rule that is unique to the US Food and Drug Administration.
- SAGE encourages developers seeking approval to engage relevant NRAs, in particular, national regulatory agencies and the regional regulatory structure (African Vaccine Regulatory Forum, AVAREF) of African countries, where Ebola vaccines are more likely to be deployed.
- SAGE acknowledges the national licensure of the vaccine GamEvac-Combi and would appreciate the submission of additional data, including the required evidence necessary to apply for prequalification status, should the developer wish to submit this. As the availability of several vaccines is generally beneficial, SAGE recommends that vaccine developers submit data in an application, as soon as they are available, to the WHO Secretariat according to established procedures (e.g., prequalification procedures).

2. Is the current evidence sufficient for SAGE to make recommendations regarding the use of Ebola vaccines in case of another Ebola outbreak (pre-licensure and/or post licensure)? If yes, which recommendations can be proposed? If not, what key data are missing?

- Should an EVD outbreak occur, SAGE recommends the use of the rVSVΔG-ZEBOV-GP candidate vaccine for which clinical efficacy data are available. As this is an unlicensed candidate vaccine to date, this candidate vaccine should be deployed under the Expanded Access framework, with informed consent and in compliance with Good Clinical Practices. The recommended delivery strategy is the ring vaccination adapted to the social and geographic conditions of the outbreak and affected areas. The Expanded Access study protocol—that is being discussed with Member States by MSF, the vaccine developer, WHO, CDC, and other partners—should be implemented promptly after the confirmation of a case of Ebola virus disease. If the emerging outbreak was caused by an Ebola virus species other than Zaire, consideration should be given to the use of other candidate vaccines that target the putative viral species. This Expanded Access should be used as an opportunity to accumulate additional information on vaccine safety, efficacy and effectiveness.
- Though SAGE recognizes the risks faced by health care workers and their potential role in the amplification of Ebola virus transmission early in an outbreak, current evidence is insufficient to

recommend pre-emptive vaccination of this group. There is incomplete information on the duration of the immune response for the vaccines that are under review, and uncertainty on vaccine cross-protection for the different Ebola virus species. There is also a need to generate more safety data on the rVSVΔG-ZEBOV-GP vaccine in African populations, noting the safety concerns of arthritis and arthralgia that occurred in the Phase 1 study in Switzerland. More finely grained sociological knowledge is required to appreciate the acceptability of vaccines used pre-emptively amongst health care workers, noting the low acceptability of Ebola vaccination by health care workers reported in Liberia. Lastly, additional modelling work should be done to refine estimates on the additional benefit of pre-emptive health care worker immunisation.

- SAGE also considers that available evidence is insufficient to recommend pre-emptive mass immunisation of the general population because of the still partial knowledge on the vaccine immunogenicity, efficacy, safety, and acceptability as well as the unpredictability of where Ebola may emerge next and the generally low attack rate observed to date in the general population. The existence of effective control interventions (including ring vaccination) when outbreaks are detected and responded to in a timely and decisive fashion is also a consideration.
- SAGE recommends that, once one or more Ebola vaccines are licensed and prequalified, a mechanism for stockpiling them should be put in place to ensure prompt and equitable access. Mathematical modelling estimates should be further refined to help inform the size and composition of the stockpile. At the present time, a stockpile of up to 300,000 doses can be recommended to cover the likely size of a large outbreak in high transmission settings.
- SAGE recommends taking all opportunities to generate or expand the evidence base that can broaden the indication and increase the acceptability of Ebola vaccination. This evidence that ongoing clinical studies, outbreak-related deployments, or operational research could generate should include:
 - Safety, immunogenicity and efficacy of candidate vaccines in population groups not generally considered in clinical trials, such as infants and young children, pregnant women, children of breastfeeding mothers, people living with HIV, and other immune compromised persons;
 - Vaccination perception and acceptability, especially among health care workers, front-line workers, and informal health care providers such as traditional healers, birth assistants, bone setters, and Ebola virus disease survivors; and
 - Social mobilization and communication research to improve messaging and communication strategies in the event of an outbreak.

5 | BIBLIOGRAPHY

1. Ebola haemorrhagic fever in Zaire, 1976. *Bull World Health Organ.* 1978;56(2):271-93.
2. WHO Ebola Response Team, Agua-Agum J, Allegranzi B, Ariyaratna A, Aylward R, Blake IM, et al. After Ebola in West Africa--Unpredictable risks, preventable epidemics. *N Engl J Med.* 2016;375(6):587-96.
3. Bausch DG, Nichol ST, Muyembe-Tamfum JJ, Borchert M, Rollin PE, Sleurs H, et al. Marburg hemorrhagic fever associated with multiple genetic lineages of virus. *N Engl J Med.* 2006;355(9):909-19.
4. Miranda ME, Miranda NL. Reston ebolavirus in humans and animals in the Philippines: a review. *J Infect Dis.* 2011;204 Suppl 3:S757-60.
5. Le Guenno B, Formenty P, Wyers M, Gounon P, Walker F, Boesch C. Isolation and partial characterisation of a new strain of Ebola virus. *Lancet.* 1995;345(8960):1271-4.
6. Heymann DL. Ebola: learn from the past. *Nature.* 2014;514(7522):299-300.
7. Deen GF, Knust B, Broutet N, Sesay FR, Formenty P, Ross C, et al. Ebola RNA Persistence in Semen of Ebola Virus Disease Survivors - Preliminary Report. *N Engl J Med.* 2015.
8. Baize S, Pannetier D, Oestereich L, Rieger T, Koivogui L, Magassouba N, et al. Emergence of Zaire Ebola virus disease in Guinea. *N Engl J Med.* 2014;371(15):1418-25.
9. Sow MS, Etard JF, Baize S, Magassouba N, Faye O, Msellati P, et al. New Evidence of Long-lasting Persistence of Ebola Virus Genetic Material in Semen of Survivors. *J Infect Dis.* 2016;214(10):1475-6.
10. Sissoko D, Duraffour S, Kerber R, Kolie JS, Beavogui AH, Camara AM, et al. Persistence and clearance of Ebola virus RNA from seminal fluid of Ebola virus disease survivors: a longitudinal analysis and modelling study. *Lancet Glob Health.* 2017;5(1):e80-e8.
11. Sissoko D, Keita M, Diallo B, Aliabadi N, Fitter DL, Dahl BA, et al. Ebola Virus Persistence in Breast Milk After No Reported Illness: A Likely Source of Virus Transmission From Mother to Child. *Clin Infect Dis.* 2016.
12. WHO Ebola Response Team, Agua-Agum J, Ariyaratna A, Blake IM, Cori A, Donnelly CA, et al. Ebola virus disease among children in West Africa. *N Engl J Med.* 2015;372(13):1274-7.
13. Khan AS, Tshioko FK, Heymann DL, Le Guenno B, Nabeth P, Kerstiens B, et al. The reemergence of Ebola hemorrhagic fever, Democratic Republic of the Congo, 1995. Commission de Lutte contre les Epidemies a Kikwit. *J Infect Dis.* 1999;179 Suppl 1:S76-86.
14. Senga M, Pringle K, Ramsay A, Brett-Major DM, Fowler RA, French I, et al. Factors Underlying Ebola Virus Infection Among Health Workers, Kenema, Sierra Leone, 2014-2015. *Clin Infect Dis.* 2016;63(4):454-9.
15. Winslow RL, Milligan ID, Voysey M, Luhn K, Shukarev G, Douoguih M, et al. Immune Responses to Novel Adenovirus Type 26 and Modified Vaccinia Virus Ankara-Vectored Ebola Vaccines at 1 Year. *Jama.* 2017;317(10):1075-7.
16. Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ca Suffit!). *Lancet.* 2017;389:505-18.

Appendix A: Characteristics of Ebolavirus and Marburg virus outbreaks with ≥4 reported human cases, 1976–2016

Legend: EBOV, species *Zaire ebolavirus*; SUDV, species *Sudan ebolavirus*; BDBV, species *Bundibugyo ebolavirus*; MARV, species *Marburg marburgvirus*

Month & year started	Country	Virus species	Weeks to 1 st peak	Weeks to extinction	Report cases	Reported deaths (CFR %)	Reference
Jun-76	South Sudan	SUDV	5	20	284	151 (53%)	WHO/International Study Team, 1978 (1)
Aug-76	Democratic Republic of Congo	EBOV	5	9	318	280 (88%)	Report of an International Commission, 1978 (2)
Jul-79	South Sudan	SUDV	2	10	34	22 (65%)	Baron et al., 1983 (3)
Nov-94	Gabon	EBOV	4	13	49	30 (61%)	Georges et al., 1999 (4)
Jan-95	Democratic Republic of Congo	EBOV	17	27	315	250 (81%)	Khan et al., 1999 (5)
Jan-96	Gabon	EBOV	0	5	29	18 (62%)	Georges et al., 1999 (4)
Jul-96	Gabon	EBOV	18	27	60	45 (74%)	Georges et al., 1999 (4)
Oct-98	Democratic Republic of Congo	MARV	13	100	154	125 (81%)	Bausch et al., 2006 (6)
Aug-00	Uganda	SUDV	5	20	425	224 (53%)	Okware et al., 2002 Trop Med Inter Health 2002 (7)
Oct-01	Gabon & Republic of Congo	EBOV	6	21	124	96 (77%)	World Health Organization, 2003 (8) Nkoghe et al., 2005 (9)
May-02	Gabon & Republic of Congo	EBOV	5	10	11	10 (90%)	World Health Organization, 2003 (8)
Dec-02	Republic of Congo	EBOV	N/A	19	143	128 (89%)	Formenty et al., 2003 (10)
Oct-03	Republic of Congo	EBOV	5	7	35	29 (83%)	Boumandouki et al., 2005 (11)
Apr-04	South Sudan	SUDV	1	10	17	7 (41%)	World Health Organization, 2005 (12)
Oct-04	Angola	MARV	24	42	252	227 (90%)	World Health Organization, 2005 (13, 14) US CDC, 2005 (15) Towner et al., 2006 (16)
Jun-07	Democratic Republic of Congo	EBOV	13	15	264	187 (71%)	World Health Organization, 2007 (17) Leroy et al., 2009 (18) Grard et al., 2011 (19)
Jun-07	Uganda	MARV	N/A	13	4	1 (25%)	Adjemian et al., 2001 (20)
Aug-07	Uganda	BDBV	14	18	149	37 (25%)	MacNeil et al., 2011 (21)
Nov-08	Democratic Republic of Congo	EBOV	3	5	32	15 (47%)	World Health Organization, 2009 (22) Rosello et al., 2015 (23)
Oct-12	Uganda	MARV	N/A	3	15	4 (27%)	Albariño et al., 2013 (24)
Aug-12	Democratic Republic of Congo	BDBV	N/A	8	36	13 (36%)	Albariño et al., 2013 (24)
Nov-12	Uganda	SUDV	N/A	1	6	3 (50%)	Albariño et al., 2013 (24)
Jul-12	Uganda	SUDV	N/A	1	11	4 (36%)	Albariño et al., 2013 (24)

Dec-13	West Africa & other countries in Africa, Europe and North America	EBOV	17	109	28,652	11,325 (40%)	WHO Ebola Response Team 2014, 2015 & 2016 (25-27)
Jul-14	Democratic Republic of Congo	EBOV	4	10	69	49 (74%)	Maganga et al., 2014 (28)

References on reported Ebolavirus and Marburg virus outbreaks

1. Ebola haemorrhagic fever in Sudan, 1976. Report of a WHO/International Study Team. Bull World Health Organ. 1978;56(2):247-70.
2. Ebola haemorrhagic fever in Zaire, 1976. Bull World Health Organ. 1978;56(2):271-93.
3. Baron RC, McCormick JB, Zubeir OA. Ebola virus disease in southern Sudan: hospital dissemination and intrafamilial spread. Bull World Health Organ. 1983;61(6):997-1003.
4. Georges AJ, Leroy EM, Renaut AA, Benissan CT, Nabias RJ, Ngoc MT, et al. Ebola hemorrhagic fever outbreaks in Gabon, 1994-1997: epidemiologic and health control issues. J Infect Dis. 1999;179 Suppl 1:S65-75.
5. Khan AS, Tshioko FK, Heymann DL, Le Guenno B, Nabeth P, Kerstiens B, et al. The reemergence of Ebola hemorrhagic fever, Democratic Republic of the Congo, 1995. Commission de Lutte contre les Epidemies a Kikwit. J Infect Dis. 1999;179 Suppl 1:S76-86.
6. Bausch DG, Nichol ST, Muyembe-Tamfum JJ, Borchert M, Rollin PE, Sleurs H, et al. Marburg hemorrhagic fever associated with multiple genetic lineages of virus. N Engl J Med. 2006;355(9):909-19.
7. Okware SI, Omaswa FG, Zaramba S, Opio A, Lutwama JJ, Kamugisha J, et al. An outbreak of Ebola in Uganda. Trop Med Int Health. 2002;7(12):1068-75.
8. Outbreak(s) of Ebola haemorrhagic fever, Congo and Gabon, October 2001-July 2002. Wkly Epidemiol Rec. 2003;78(26):223-8.
9. Nkoghe D, Formenty P, Leroy EM, Nnegue S, Edou SY, Ba JI, et al. [Multiple Ebola virus haemorrhagic fever outbreaks in Gabon, from October 2001 to April 2002]. Bull Soc Pathol Exot. 2005;98(3):224-9.
10. Formenty P, Libama F, Epelboin A, Allarangar Y, Leroy E, Moudzeo H, et al. [Outbreak of Ebola hemorrhagic fever in the Republic of the Congo, 2003: a new strategy?]. Med Trop (Mars). 2003;63(3):291-5.
11. Boumandouki P, Formenty P, Epelboin A, Campbell P, Atsangandoko C, Allarangar Y, et al. [Clinical management of patients and deceased during the Ebola outbreak from October to December 2003 in Republic of Congo]. Bull Soc Pathol Exot. 2005;98(3):218-23.
12. Outbreak of Ebola haemorrhagic fever in Yambio, south Sudan, April - June 2004. Wkly Epidemiol Rec. 2005;80(43):370-5.
13. Marburg haemorrhagic fever, Angola. Wkly Epidemiol Rec. 2005;80(18):158-9.
14. World Health Organization. Marburg haemorrhagic fever in Angola – update 26: MOH declares outbreak over. Geneva, Switzerland: World Health Organization; 2005 [Available from: http://www.who.int/csr/don/2005_11_07a/en/].
15. Outbreak of Marburg virus hemorrhagic fever--Angola, October 1, 2004-March 29, 2005. MMWR Morb Mortal Wkly Rep. 2005;54(12):308-9.
16. Towner JS, Khristova ML, Sealy TK, Vincent MJ, Erickson BR, Bawiec DA, et al. Marburgvirus genomics and association with a large hemorrhagic fever outbreak in Angola. J Virol. 2006;80(13):6497-516.
17. Outbreak news. Ebola virus haemorrhagic fever, Democratic Republic of the Congo--update. Wkly Epidemiol Rec. 2007;82(40):345-6.
18. Leroy EM, Epelboin A, Mondonge V, Pourrut X, Gonzalez JP, Muyembe-Tamfum JJ, et al. Human Ebola outbreak resulting from direct exposure to fruit bats in Luebo, Democratic Republic of Congo, 2007. Vector Borne Zoonotic Dis. 2009;9(6):723-8.

19. Grard G, Biek R, Tamfum JJ, Fair J, Wolfe N, Formenty P, et al. Emergence of divergent Zaire ebola virus strains in Democratic Republic of the Congo in 2007 and 2008. *J Infect Dis.* 2011;204 Suppl 3:S776-84.
20. Adjemian J, Farnon EC, Tschiko F, Wamala JF, Byaruhanga E, Bwire GS, et al. Outbreak of Marburg hemorrhagic fever among miners in Kamwenge and Ibanda Districts, Uganda, 2007. *J Infect Dis.* 2011;204 Suppl 3:S796-9.
21. MacNeil A, Farnon EC, Morgan OW, Gould P, Boehmer TK, Blaney DD, et al. Filovirus outbreak detection and surveillance: lessons from Bundibugyo. *J Infect Dis.* 2011;204 Suppl 3:S761-7.
22. World Health Organization. End of Ebola outbreak in the Democratic Republic of the Congo Geneva, Switzerland: World Health Organization; 2009 [updated 17/02/2009. Available from: http://www.who.int/csr/don/2009_02_17/en/.
23. Rosello A, Mossoko M, Flasche S, Van Hoek AJ, Mbala P, Camacho A, et al. Ebola virus disease in the Democratic Republic of the Congo, 1976-2014. *Elife.* 2015;4.
24. Albarino CG, Shoemaker T, Khristova ML, Wamala JF, Muyembe JJ, Balinandi S, et al. Genomic analysis of filoviruses associated with four viral hemorrhagic fever outbreaks in Uganda and the Democratic Republic of the Congo in 2012. *Virology.* 2013;442(2):97-100.
25. WHO Ebola Response Team. Ebola virus disease in West Africa--the first 9 months of the epidemic and forward projections. *N Engl J Med.* 2014;371(16):1481-95.
26. WHO Ebola Response Team, Agua-Agum J, Ariyaratna A, Aylward B, Blake IM, Brennan R, et al. West African Ebola epidemic after one year--slowing but not yet under control. *N Engl J Med.* 2015;372(6):584-7.
27. WHO Ebola Response Team, Agua-Agum J, Allegranzi B, Ariyaratna A, Aylward R, Blake IM, et al. After Ebola in West Africa--Unpredictable risks, preventable epidemics. *N Engl J Med.* 2016;375(6):587-96.
28. Maganga GD, Kapetshi J, Berthet N, Kebela Ilunga B, Kabange F, Mbala Kingebeni P, et al. Ebola virus disease in the Democratic Republic of Congo. *N Engl J Med.* 2014;371(22):2083-91.

Appendix B: Summary of published data on efficacy, immunogenicity and safety of candidate Ebola vaccines in clinical development

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
Ad5 expressing envelope GP of Zaire Ebola virus species (Makona variant, monovalent) with or without homologous boost							
Zhu et al., 2015 (1) Li et al., 2016 (2) (PMID: 25817373 and 28017642 ; NCT02326194 and NCT02533791)	1	China	120 healthy adults aged 18-60y; both men and women, but not pregnant or breast-feeding women. 60% participants had pre-existing Ad5 immunity (titres >1:200).	Randomised, placebo-controlled, double-blind trial; 1:1:1 randomisation to 1.6x10 ¹¹ , 4.0x10 ¹⁰ viral particles [vp], or placebo; follow-up to 168d (5.6m); unmasking after preliminary analysis. At 168d, 110 participants re-recruited and received 2nd dose of same intervention (the same vaccine & dose, or placebo; follow-up to 12m (18m after 1st dose). Enrolment 12/2014–1/2015.	After priming: Glycoprotein (GP) specific antibody titres were significantly increased at d14 and d28 in both vaccine groups; they peaked at d28 and persisted by d168. T-cell responses peaked at d14 in both vaccine groups. Immunogenicity was greater in high-dose than in low-dose vaccine group. After boosting: >20-fold increase in titres at d28 in both vaccine groups; titres persisted at m18. At lower dose, immunogenicity seemed more vulnerable to pre-existing Ad5 immunity. Boosting provided greater antibody response, possibly with longer duration.	Mild and moderate solicited adverse reactions within 7d of vaccination reported at higher rate in both vaccine groups. No serious events recorded.	Completed
Zhu et al., 2016 (3) (PMID: 28017399 ; PACTR201509001259869)	2	Sierra Leone	500 healthy adults aged 18-50y; both men and women, but not pregnant or breast-feeding women; HIV	Randomised, placebo-controlled, double-blind trial; 2:1:1 randomisation to 8.0x10 ¹⁰ , 1.6x10 ¹¹ vp, or placebo; safety follow-up at 7d, immunogenicity follow-up at d14, 28 and	GP-specific antibodies detected from d14, peaked at d28, and later declined by d168 (still approx. 40-fold greater than in placebo group). Although immunogenicity was greater	Rates of ≥1 adverse reaction within 7d of vaccination were similar in 3 groups; most reactions mild and	Completed

Ebola vaccines — Background paper for SAGE deliberations

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
Ad5 expressing envelope GP of Sudan and Zaire Ebola virus species (bivalent)							
Ledgerwood et al., 2010 (4) (PMID: 21034824 ; NCT00374309)	1	USA (Maryland)	31 healthy adults, both men and women; mean age 31y. Half of participants had a high level of pre-existing Ad5 immunity (titres >1:500)	Randomised, placebo-controlled, double-blind trial; 3: 1 randomisation to either 2x10 ¹¹ or 2x10 ¹⁰ vp and placebo; follow-up for 48w. Enrolment 9/2006–11/2007.	Actual randomization 11:12:8. Sudan and Zaire GP-specific seropositivity peaked at 58% and 50% at w4 and was 42% and 33% at w48, respectively; response rates were higher in low-dose vaccine group, but magnitudes were non-statistically higher in high-dose group. Ad5-seronegative vaccinees had significantly higher response rates and magnitude of response than Ad5-seropositive vaccinees. Sudan and Zaire GP-specific T-cell responses were present in both low- and high-dose vaccinees.	Self-limited reactivity without sequelae was observed. Three adverse events related to vaccination (two cases of partial thromboplastin time, a case of Grade 3 fever with 24h).	Completed
			negative, no EVD history, no previous Ebola immunisation. 45% participants had pre-existing Ad5 immunity (titres >1:200).	168. Enrolment 10/2015.	in high-dose than in low-dose vaccine group, candidate vaccine was highly immunogenic at both dose levels in healthy Sierra Leonean adults. Lower dosage was chosen for further development also on basis of results from preclinical animal studies.	self-limiting. Injection-site reactions were more frequent in vaccine groups. No serious events related to vaccine.	

Ebola vaccines — Background paper for SAGE deliberations

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
Ad26 expressing envelope GP of Zaire Ebola virus species (Mayinga variant, as prime) and modified vaccinia Ankara expressing 4 filoviruses nucleoproteins (MVA-BN-Filo, as boost)							
Milligan et al., 2016 (5) Winslow et al., 2017 (6) (PMID: 27092831 ; NCT02313077)	1	United Kingdom (Oxford)	87 healthy adults aged 18–50y (median age 38.5y); both men and women, but not pregnant or breast-feeding women; 67% participants were women. 3.4% participants had pre-existing Aq26 immunity (titres threshold not defined).	Randomised, placebo-controlled, observer-blind trial; 5:1 randomisation, with 4 vaccine groups (72 participants): primed with either Ad26 5×10 ¹⁰ vp or MVA 1×10 ⁸ infective dose and boosted with alternative vaccine at either d28 or d56. Also, open-label trial; 15 participants primed with Ad26 and boosted by MVA at d14. Follow-up for 12m after priming. Enrolment 12/2014–2/2015.	Seropositivity at d28 in 97% and 23% vaccinees primed with Ad26 and MVA, respectively; all vaccinees had detectable GP-specific IgG at d21 after boost and at 8m and 12m follow-ups. 60–83% vaccinees had T-cell persistent response at m12. Conclusion was that Ad26 priming induces immune response and MVA boosting sustained and specific immunity.	In randomised groups, 5% participants experienced fever after Ad26, none after MVA. In open-label group, 27% experienced fever. No vaccine-related serious adverse events occurred.	Completed
Enria et al., 2016 (7) (PMID: 27821112 ; NCT02509494)	3	Sierra Leone (Kambia)	Stage 1: 43 healthy adults aged ≥18y. Stage 2: 688 persons aged ≥1y.	Study denominated EBOVAC-Salon; reported as phase 3 trials, but stage description only reports safety/immunogenicity evaluation. Stage 1: open label, primed with Ad26 5×10 ¹⁰ vp and boosted with MVA 1×10 ⁸ infective dose at d28; vaccinated from 10/2015. Stage 2: randomised, controlled, double-blind trial; randomization to same prime/boost regimen as	N/A	N/A	Currently recruiting. Data collection for primary outcome measure finalized by 9/2018.

Ebola vaccines — Background paper for SAGE deliberations

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
ChAd3 expressing envelope GP of Zaire Ebola virus species (Mayinga variant, monovalent)							
De Santis et al., 2016 (8) (PMID: 26725450 ; NCT02289027)	1/2a	Switzerland (Lausanne)	120 healthy adults aged 18–65y. Also, individual potentially deployable to areas with ongoing transmission.	Randomised, placebo-controlled, double-blind, dose-finding trial; 2:2:1 randomisation to ChAd3-EBOZ 2.5×10 ¹⁰ (low dose), 5×10 ¹⁰ (high dose) or placebo. Allocation not concealed for deployable participants. Follow-up for 180d. Enrolment 10/2014–6/2015.	GP-specific antibody response rate in vaccinees was 96% (5% in placebo). Ab-level peaked at d28 and halved by d180. CD4/8 cell responses were 60–70%. ChAd3-EBO-Z was safe and well tolerated, although mild/moderate systemic adverse events were common. No significant differences related to two dosages.	>75% vaccinees reported local adverse events. Fatigue or malaise was most reported systemic event (60%) and 25–30% vaccinees reported fever within 24h after vaccination. No serious vaccine-related adverse events reported.	Completed
Tapia et al., 2016 (9) (PMID: 26546548 ; NCT02231866)	1	USA (Maryland)	20 healthy participants aged 18–65y. Both sexes	Randomized, single-blind trial. 1:1 randomisation to ChAd3 (monovalent) 1×10 ¹⁰ or 1×10 ¹¹ vp. Follow-up for 180d. Enrolment 11/2014.	100% vaccinees of both dose levels showed humoral response at d28. Titres were >2-fold higher in higher-dose group.	Local pain and tenderness, fatigue and headache were most frequently reported adverse	Completed

Ebola vaccines — Background paper for SAGE deliberations

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
ChAd3 (monovalent) boosted with MVA–BN–Filo							
Ewer et al., 2016 (10) (PMID: 25629663 ; NCT02240875)	1	UK (Oxford)	76 healthy adults aged 18–50y.	Open-label trial. <i>Priming:</i> 20:36:20 participants each received ChAd3 at 1×10^{10} , 2.5×10^{10} and 5×10^{10} vp. <i>Boosting:</i> 46 participants in total boosted with MVA. At w1–2, 16 participants of ChAd3 2.5×10^{10} dose boosted with MVA 1.5×10^8 plaque forming units (pfu). At w3–10, 10 participants of 3 ChAd3 dose groups boosted at either MVA 1.5×10^8 (18 participants) or 3×10^8 (12), stratified per priming dose group. Follow-up for 29d (primed only) or 180d (if boosted). Also, comparison of neutralizing antibody activity with that observed in ph1 trial of rVSV-ZEBOV. Enrolment in late 2014.	After MVA boost, GP-specific antibody response increased by d7 compared to pre-boost level, peaked at d14, and remained higher at d180 days. At w4, MVA boosting also increased virus-specific (12-fold) and neutralizing antibodies titres and CD8 cell response (5-fold). At d180, 100% boosted and less than half primed-only vaccinees remained positive for GP-specific antibodies; titres in boosted were 4-fold greater. ChAd3 boosted with MVA elicited humoral and cellular immune responses that were superior to those induced by ChAd3 alone	Majority of adverse events were self-limited and mild. Moderate systemic adverse events included fever, myalgia, arthralgia, headache, fatigue, nausea and malaise. No severe systemic solicited adverse reported. No safety concerns were identified at any of the dose levels studied.	Completed
Tapia et al., 2016 (9) (PMID: 26546548 ; NCT02267109)	1b	Mali	91 adults aged 18–50y (52 participants boosted with either MVA–BN–Filo [27] or saline	Open-label and double-blind, dose-escalation trial (ChAd3 prime); nested, randomised, placebo-controlled and double-blind trial (MVA boost).	83–100% vaccinees showed humoral response after ChAd3 at d28, unrelated to dose level. 100% vaccinees showed humoral response after MVA boost at both d7	Most adverse events were mild. Predominant solicited adverse event was fever (10/11 episodes	Completed

Ebola vaccines — Background paper for SAGE deliberations

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
ChAd3 expressing envelope GP of Zaire (Mayinga variant) and Sudan Ebola virus species (bivalent) Lederwood et al., 2014 & 2017 (11, 12) (PMID: 25426834 ; NCT02231866)	1	USA (Maryland)	[25]. Males & females not breast-feeding, not pregnant & not planning to become pregnant.	1:3:3:1 randomisation to ChAd3 1×10^{10} , 2.5×10^{10} , 5×10^{10} or 1×10^{11} vp. 52 participants were further 1:1 randomised to boost MVA 2×10^8 pfu or placebo. Follow up for 180d after primary or booster vaccination. Enrolment 11/2014 (prime) and 2/2015 (boost).	and d28. T-cell responses after ChAd3 priming were of small magnitude, but stable at time of boosting. In contrast, cellular response was high-magnitude in 85% after boosting. Results suggest use of 1×10^{11} ChAd3 dose for reactive vaccination and MVA boosting for conferring long-lived protection.	resolved within 24h). Only one serious event observed in a Malian participant, but deemed unrelated to vaccine.	Completed
DNA plasmid vaccines Martin et al., 2006 (13) (PMID: 16988008 ; NCT00072605)	1		20 healthy participants aged 18–50, both sexes (55% women)	Open-label, dose-escalation trial. Participants sequentially enrolled in groups of 10 to receive ChAd3 (bivalent) at doses 2×10^{10} and 2×10^{11} vp. Followed-up for 48w. Enrolment 9/2014.	At w4, 90/100%, 90/90% & 70/80% vaccinees showed Zaire/Mayinga, Zaire/Makona & Sudan GP-specific humoral response (low/high dose), respectively. At w48, Zaire/Mayinga titres remained elevated. T-cell responses were dose-dependent (20-80% at w4 & 10-50% at w8). Pre-existing ChAd3 & Ad5 antibodies had no correlation with immune responses.	No safety concerns were identified. Fever reported in 2 participants in higher dose group. No serious adverse events were reported.	Completed
			27 healthy adults aged 18–44 years	1st generation DNA vaccine, protocol VRC 204. Three-plasmid DNA vaccine encoding GP from	100% vaccinees showed GP-specific humoral and cellular responses detected at 4w after 3rd dose. Responses	Vaccine was well-tolerated, with no significant adverse events.	Completed in 8/2005

Ebola vaccines — Background paper for SAGE deliberations

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
Kibuuka et al., 2015 (14) (PMID: 25540891 ; NCT00997607)	1b	Uganda (Kampala)	108 healthy adults aged 18– 50y	Zaire and Sudan/Gulu species and nucleoprotein (VRC-EBODNA012-00-VP). Randomized, controlled, double-blind trial. 5:8:8:6 randomization to three injections (d0, d28, d56) of vaccine at doses 2, 4, 8mg or placebo. Followed for 12m. Enrollment in 11/2003–7/2004.	were also detectable after 2nd dose. Results of cellular responses also reported. Candidate DNA vaccine was immunogenic.	Vaccines were well tolerated. No significant differences in local or systemic reactions observed between groups.	Completed
Sarwar et al., 2015 (15) (PMID: 25225676 ; NCT00605514)	1	USA (Maryland)	20 healthy adults aged 18–60 y	Two DNA plasmid vaccines: one encoding Zaire and Sudan Ebola virus species GP (EBO, VRC-EBODNA023-00-VP) and one Marburg virus (MAR, VRC-MARDNA025- 00-VP). Randomised, placebo-controlled, double-blind trial. 5:1 randomization to 3 injections of vaccine or placebo at d0, w4 and w8, with vaccine allocations divided equally b/w EBO only, MAR only, and both. Follow-up for 2y. Enrolled 11/2009–4/2010.	GP-specific humoral and T- cell immune responses were similar between separate and concomitant use of two vaccines at w4 after 3rd dose (humoral: approx. 50% EBO and 25% MAR; cellular: 30–60% EBO and 40–50% MAR). Both vaccines given alone or jointly elicited antigen immune responses. Responses were not cross- reactive between EBO and MAR vaccines.	Vaccines were well tolerated and no serious adverse events	Completed

Ebola vaccines — Background paper for SAGE deliberations

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				homologous boost at ≥w32. Follow-up for 32/44w (w/o or w/ boost). Enrolled 6/2008–6/2009.	decreased at w24. Cellular responses observed at less frequently (CD4+ T-cell 13–30% at w4 after 3rd dose). 4th dose boosted humoral response to near peak levels and T-cell responses slightly.	were reported.	
GamEvac-Combi (rVSV & Ad5, prime & heterologous boost) expressing Zaire Ebola virus species (Makona variant)							
Dolzhiikova et al., 2017 (16) (PMID: 28152326 ; zakupki.gov.ru no. 0373100043 215000055)	1/2	Russia	84 healthy adults aged 18–55y, both sexes (76% men)	Open-label, dose-escalation trial. GamEvac-Combi candidate vaccine (rVSV prime & heterologous Ad5 boost), each component alone or in combination at full (rVSV 2.5x10 ⁷ pfu & Ad5 2.5x10 ¹¹ vp) or half dose. For safety evaluation, an initial group was assigned to receive either rVSV (12 participants) or Ad5 (12) at half dose. For safety and immunogenicity evaluation, a second group of 60 participants received rVSV followed by Ad5 at d21 at either full or half dose. Followed up for 42d. Enrolment 9–11/2015.	100% prime-boost vaccinees of both dose groups showed GP-specific immune response at d42. Titres were 1.25-fold greater in full-dose vaccinees at d42 compared to half-dose vaccinees. In full-dose vaccinees, titres were 5-fold lower in rVSV-only vaccinees compared to prime-boost vaccinees. Pre-existing neutralizing Ad5 antibodies adversely influenced GP-specific response in half-dose group, but not in full-dose group. 93% prime-boost vaccinees in full-dose group showed neutralizing Mayinga, taken as indication of cross-reactive immunogenicity from Makona. 59–83% prime-boost vaccinees of both dose groups showed T-cell responses at d28, with	Pain at the injection site was most frequently reported adverse event. No serious adverse event was reported.	Completed

Ebola vaccines — Background paper for SAGE deliberations

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
Only information from clinical trial registry entry (Gamaleay Research Institute, Russia) (PMID: N/A; NCT02911415 & NCT02911428)	4	Russia	120 healthy adults aged 18–56y, both sexes. 60 participants each as Ad5 prime only (NCT02911428) or rVSV prime & Ad5 boost (NCT02911415)	Both candidate vaccines GamEvac (Ad5 prime only, protocol 02-E-2015) & GamEvac-Combi (rVSV prime and Ad5 boost, protocol 01-COMBI-2015). Observational, prospective cohort study to evaluate duration of immunity after earlier vaccination (that occurred 10–11/2015) at two dose levels. Follow-up visits at 12, 18 & 24m after vaccination. Enrolment from 10/2016.	lower percentages at d42. Vaccine showed high immunogenicity and had good safety profile. Accordingly, it was registered in Russia in 12/2015. Primary outcome measures relate to immunogenicity and safety. Study started in 10/2016, final data collection for primary outcome measure by 12/2017.	N/A	Ongoing; data collection for primary outcome measure finalized by 12/2017.
Russian Federation MOH briefing at WHO Executive Board meeting of 2/2016 (PMID: N/A; NCT03072030 & PACTR201702002053400)	2	Guinea (Kindia)	2,000 healthy adults aged 18–60y, both sexes	Candidate vaccine GamEvac-Combi: rVSV prime, 2.5x10 ⁷ pfu; Ad5 boost at d21, 2.5x10 ¹¹ vp. Randomized, placebo-controlled, double-blind trial. 19:1 randomization to either prime/boost (1,900 participants) or placebo (100). According to epidemiological	Primary objective relates to immunogenicity. If an outbreak was to occur, efficacy would also be assessed.	N/A	Not yet recruiting. Anticipated study start 6/2017; data collection for primary outcome measure finalized by 6/2019.

Ebola vaccines — Background paper for SAGE deliberations

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
rVSV expressing envelope GP of Zaire Ebola virus species (Mayinga variant, rVSVAG-ZEBOV-GP) with or without homologous boost				situation, option for ring vaccination around confirmed EVD cases. Follow-up for 12m. Enrolment expected from 7/2017.			
Agnandji et al., 2016 (17) (PMID: 25830326 ; NCT02283099 , NCT02287480 , NCT02296983 , and PACTR201411000919191)	1	Africa (Lambaréné, Gabon; Kilifi, Kenya) and Europe (Hamburg, Germany; Geneva, Switzerland)	<i>Gabon, Kenya, Germany:</i> 99 healthy adults aged 18–55y, both sexes (75% men). <i>Switzerland:</i> 59 healthy adults aged 18–65y, both sexes (61% men)	<i>Gabon, Kenya, Germany:</i> Open-label, uncontrolled, dose-escalation trial of single rVSV dose at 3×10^5 – 2×10^7 pfu. <i>Switzerland:</i> randomized, placebo-controlled, double-blind trial at rVSV doses 1 – 5×10^7 pfu; first 19 participants open-label at 1×10^7 pfu, then 1:1 randomization to 1×10^7 or 5×10^7 pfu for deployable participants or 1:1:1 randomization to 1×10^7 , 5×10^7 pfu or placebo for non-deployable participants; unmasked after 3m. Follow-up for 28d (safety) and 180d (immunogenicity). Enrolled 11/2014–1/2015.	All vaccinees showed GP-specific antibody responses; similar titres for different doses that were sustained at 180d. Most vaccinees showed neutralizing antibodies, with higher titres at higher doses.	Within 1st day, mild-to-moderate adverse events, with fever being most frequent (up to 30% vaccinees). In 2nd week, 11/51 (22%) Geneva participants showed arthritis affecting 1–4 joints with 8d median duration, but only 2 (3%) vaccinees did at other three trial sites. No serious vaccine-related adverse events reported.	Completed (Germany, Switzerland); recruitment completed, but study ongoing (Gabon, Kenya)
Huttner et al., 2015 (18) (PMID: 26248510 ; NCT02287480)	1/2	Switzerland (Geneva)	67 healthy adults aged 18–65 years, of which 38 individuals were potentially	Randomised, placebo-controlled, double-blind trial. Non-deployable participants 5:1 randomised to rVSV dose	For preliminary results, see Agnandji et al., 2016; here interim results reported. Similar seropositivity rates were similarly (>90%), but	Mild, early-onset reactogenicity reported in 88%, 98% and 15% of low-, high-dose	Completed

Ebola vaccines — Background paper for SAGE deliberations

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
Regules et al., 2015 & 2017 (19, 20) (PMID: 25830322 ; NCT02269423 and NCT02280408)	1	USA (Maryland)	deployable to areas with ongoing transmission	5x10 ⁷ (9 participants), 1x10 ⁷ (17), 3x10 ⁵ pfu (38) or placebo (13); open-label for 38 deployable participants at 3 dose levels (13 at lowest dose). Follow-up for 12m. Enrolment 1/2015.	GP-specific and neutralising Ab titres were 3 times lower in low-dose versus high-dose vaccinees. Lowering rVSV dose improved early tolerability, but also lowered antibody responses and did not prevent vaccine-induced arthritis, dermatitis, or vasculitis.	and placebo participants, respectively. 25% vaccinees at dose 1x10 ⁷ pfu w/ had objective fever. 25% low-dose vaccinees experienced oligoarthritis with median onset d10, associated with increasing age. No serious adverse events reported.	Completed
Ebola ça suffit ring vaccination trial consortium, 2015 (21) Henao-Restrepo et al., 2015 & 2017 (22, 23)	3	Guinea, Sierra Leone	78 healthy adults aged 18–50y, both sexes (71% men)	Placebo-controlled, double-blind, dose-escalation trial. Consecutive enrolment to 3x10 ⁶ , 2x10 ⁷ and 1x10 ⁸ pfu (60 participants) or placebo (18). At one of two sites, participants received 2nd dose at d28. Follow-up for 28d (after either 1st or 2nd injection). Enrolment 10/2014–1/2015. <i>Cluster-randomized trial: Ebola Ça Suffit!</i> trial. <i>Cluster-randomized (ring) trial: single rVSV dose of 2x10⁷ pfu; randomization</i>	100% vaccinees seroconverted for GP-specific antibodies by d28. Higher titres in vaccinees with two higher dose levels. 2nd dose at d28 increased titres by d56, but titres were diminished at 6m. Results support for further evaluation of rVSV at dose 2x10 ⁷ pfu and indicate that 2nd dose boost antibody responses. <i>Cluster-randomized trial: Vaccine efficacy was 100.0% (95% CI: 68.9–100.0%). Front-line worker trial: Only</i>	Injection-site pain, fatigue, myalgia, and headache were reported most frequently. Rates of adverse events were lower after 2nd dose. No serious adverse events observed. <i>Cluster-randomized trial: 54% of participants reported at ≥1</i>	Completed

Ebola vaccines — Background paper for SAGE deliberations

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
Soumah et al., 2016 (24) (PMID: 26215666 26248676 & 28017403 ; PACTR201503001057193)			clusters in communities with confirmed EVD. Initially aged ≥18y and not pregnant, breastfeeding, or severely ill; later age lowered to ≥6y. Both sexes (60% women) 2,016 healthy adults, front-line workers aged ≥18y. Both sexes (75% men)	by cluster into immediate or 21d delayed vaccination. No immunological testing. Follow up for 84d. Enrolled 3/2015–1/2016. <i>Front-line worker trial:</i> non-randomized, open-label trial for safety and immunogenicity; subgroup w/ immunological assessment (112 participants): 5 blood drawings (at inclusion and w2, 4, 12, 24). Follow-up for 24w. Enrolled 4–8/2015.	preliminary results are available. 29% and 70% of participants were whole virion ELISA positive at d0 and 28, respectively; 0% and 8% showed cellular response at d0 and 28, respectively.	adverse event in 14d after vaccination; 88% of all adverse events were mild; 80 serious adverse events were identified, of which two were judged to be related to vaccination. <i>Front-line worker trial:</i> 70% participants reported adverse events. Headache and fatigue were most frequently reported. No serious adverse event was vaccine-related.	<i>Front-line worker trial:</i> recruitment completed, but study ongoing
Widdowson et al., 2016 (25) Goldstein et al., 2016 (26) (PMID: 27387395 & N/A; NCT02378753)	2/3	Sierra Leone	8,600 clinical and nonclinical workers and other Ebola frontline workers (e.g., surveillance, burial, and ambulance	STRIVE trial (Sierra Leone Trial to introduce a Vaccine against Ebola). Single rVSV dose of 2x10 ⁷ pfu. Initially planned as modified stepped-wedge trial: facilities randomized to receive vaccine at a specified time over a 6m	Preliminary data indicated 8,016 vaccinees in 5 districts, of whom 4,190 (52%) immediately vaccinated. 64 participants became EVD suspect, but 60 who gave sample tested all negative. 539 participants enrolled in immunogenicity sub-study,	No serious vaccine-related adverse events or deaths report among vaccinees. Safety profile similar to published studies.	Recruitment completed, but study ongoing

Ebola vaccines — Background paper for SAGE deliberations

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
			personnel)	period. Implemented as individually randomized trial of workers assigned to receive vaccine immediately or delayed by 18–24w. Follow-up monthly for 6m. Two sub-studies: safety in 400 participants (200 vaccinees, 200 placebo) 5 times within 28d post-vaccination; immunogenicity in 500 participants with 4 blood drawings up to 12m post-vaccination. Enrolled 4–8/2015, delayed vaccination completed in 12/2015.	but testing ongoing.		
Günther et al., 2011 (27) (PMID: 21987751 ; N/A)	N/A	USA	1 (post -exposure vaccination of biosafety level 4 laboratory worker)	Case report related to emergency vaccination of BL4 worker who got a needlestick injury with syringe containing Zaire Ebola virus species; single dose of rVSV 5.3x10 ⁷ pfu 48h after accident.	Person remained healthy. Except for the glycoprotein gene expressed in the vaccine, Ebola virus was never detected in serum and peripheral blood mononuclear cells during 3w observation period.	Patient developed fever and myalgia 3d after accident (1d after vaccination).	N/A
Lai et al., 2015 (28) (PMID: 25742465 ; N/A)	N/A	USA	1 (post -exposure of vaccination of HCW)	Case report related to emergency vaccination of a physician who got a needlestick injury while working in an Ebola treatment unit in Sierra	Ebola virus glycoprotein gene (both included in the vaccine) but Cytokine secretion and T lymphocyte and plasmablast activation were detected shortly after	Fever and moderate to severe symptoms observed 12h after vaccination and lasted 3-4d.	N/A

Ebola vaccines — Background paper for SAGE deliberations

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				Leone in 9/2014. Vaccine administered 43h after accident	vaccination. Later, GP-specific antibodies and T cells were detected, but not antibodies against Ebola viral matrix protein 40 (not generated from vaccine). PCR was consistently negative for Ebola virus nucleoprotein gene (not in the vaccine).		
rVSV expressing envelope GP of Zaire Ebola virus species (Mayinga variant, rVSV N4CT1 EBOVGP1)							
Matassov et al., 2016 (29) (PMID: N/A; NCT02718469)	1	USA	39 healthy adults, aged 18–55, both sexes	Randomized, placebo-controlled, double-blind, truncated dose escalation trial. 10:3 randomization in 3 groups to either vaccine (at doses 2.5x10 ⁴ , 2.5x10 ⁵ & 2.0x10 ⁶ pfu for each group) or placebo. Second dose administered at 28d interval. Follow-up for 26w (4m). Enrolment early 2016.	Preliminary results are from still blinded groups. GP-specific antibody responses detected in 10/13, 9/12 & 10/13 participants in low-, mid- and high-dose groups, respectively. Similarly, T cell responses detected in 8/13, 8/12 & 9/13 participants.	Adverse events across all dose groups were generally mild. Most frequently reported events were pain at injection (13/39) and fatigue (5/39).	Completed
Multiple vaccines (Ad26, ChAd3, MVA [MVA-BN-Filo], rVSV [rVSVΔG-ZEBOV-GP])							
Kennedy et al., 2016 (30) Bolay, 2016 (31) (PMID: 26768572 & N/A; NCT02344407)	2	Liberia	1,500 healthy adults aged ≥18y; not pregnant or breastfeeding or EDV history (median age 30y, 37% female)	PREVAIL-I, as part of Partnership for Research on Ebola Vaccines in Liberia. Originally also intended as Phase 3 trial (w/ enrolment of 28,000 participants). Randomisation 1:1:1 to ChAd3 and rVSV, and	At 1m post-vaccination, ChAd3 and rVSV immunogenic for 87% and 94% participants, respectively. At enrolment, 6.3% of participants had Ebola virus antibodies, but no reported EVD. 98.6% completed follow-up, which	Both vaccines well-tolerated; differences in report of adverse events between 2 vaccine and placebo groups after 1w, but not after 1m.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
Published reference N/A (PMID: N/A; NCT02876328)	2/3	Guinea & Liberia	4,900 healthy persons aged ≥1y; not pregnant, breast-feeding, EDV history, Ebola vaccination or HIV-positive	placebo; follow-up 8–12m. Enrollment 2–4/2015. PREVAC (Partnership for Research on Ebola Vaccinations). Randomization to Ad26, MVA, rVSV (single or boost at 56d), placebo. Follow-up for 12m and possibly 5y.	ended in 4/2016. Primary outcome measures relate to immunogenicity. Study start in 1/2017, final data collection for primary outcome measure by 9/2018.	N/A	Not yet recruiting; data collection for primary outcome measure finalized by 9/2018.

References for the data on efficacy, immunogenicity and safety of candidate Ebola vaccines in clinical development

- Zhu FC, Hou LH, Li JX, Wu SP, Liu P, Zhang GR, et al. Safety and immunogenicity of a novel recombinant adenovirus type-5 vector-based Ebola vaccine in healthy adults in China: preliminary report of a randomised, double-blind, placebo-controlled, phase 1 trial. *Lancet*. 2015;385(9984):2272-9.
- Li JX, Hou LH, Meng FY, Wu SP, Hu YM, Liang Q, et al. Immunity duration of a recombinant adenovirus type-5 vector-based Ebola vaccine and a homologous prime-boost immunisation in healthy adults in China: final report of a randomised, double-blind, placebo-controlled, phase 1 trial. *Lancet Glob Health*. 2017;5(3):e324-e34.
- Zhu FC, Wurie AH, Hou LH, Liang Q, Li YH, Russell JB, et al. Safety and immunogenicity of a recombinant adenovirus type-5 vector-based Ebola vaccine in healthy adults in Sierra Leone: a single-centre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet*. 2017;389(10069):621-8.
- Ledgerwood JE, Costner P, Desai N, Holman L, Enama ME, Yamshchikov G, et al. A replication defective recombinant Ad5 vaccine expressing Ebola virus GP is safe and immunogenic in healthy adults. *Vaccine*. 2010;29(2):304-13.
- Milligan ID, Gibani MM, Sewell R, Clutterbuck EA, Campbell D, Pledsted E, et al. Safety and Immunogenicity of Novel Adenovirus Type 26- and Modified Vaccinia Ankara-Vectored Ebola Vaccines: A Randomized Clinical Trial. *Jama*. 2016;315(15):1610-23.
- Winslow RL, Milligan ID, Voysey M, Luhn K, Shukarev G, Douoguih M, et al. Immune Responses to Novel Adenovirus Type 26 and Modified Vaccinia Virus Ankara-Vectored Ebola Vaccines at 1 Year. *Jama*. 2017;317(10):1075-7.
- Enria L, Lees S, Smout E, Mooney T, Tengbeh AF, Leigh B, et al. Power, fairness and trust: understanding and engaging with vaccine trial participants and communities in the setting up the EBOVAC-Salone vaccine trial in Sierra Leone. *BMC Public Health*. 2016;16(1):1140.

8. De Santis O, Audran R, Pothin E, Warpelin-Decrausaz L, Vallotton L, Wuerzner G, et al. Safety and immunogenicity of a chimpanzee adenovirus-vectored Ebola vaccine in healthy adults: a randomised, double-blind, placebo-controlled, dose-finding, phase 1/2a study. *Lancet Infect Dis.* 2016;16(3):311-20.
9. Tapia MD, Sow SO, Lyke KE, Haidara FC, Diallo F, Doumbia M, et al. Use of ChAd3-EBO-Z Ebola virus vaccine in Malian and US adults, and boosting of Malian adults with MVA-BN-Filo: a phase 1, single-blind, randomised trial, a phase 1b, open-label and double-blind, dose-escalation trial, and a nested, randomised, double-blind, placebo-controlled trial. *Lancet Infect Dis.* 2016;16(1):31-42.
10. Ewer K, Rampling T, Venkatraman N, Bowyer G, Wright D, Lambe T, et al. A Monovalent Chimpanzee Adenovirus Ebola Vaccine Boosted with MVA. *N Engl J Med.* 2016;374(17):1635-46.
11. Ledgerwood JE, DeZure AD, Stanley DA, Novik L, Enama ME, Berkowitz NM, et al. Chimpanzee Adenovirus Vector Ebola Vaccine - Preliminary Report. *N Engl J Med.* 2014.
12. Ledgerwood JE, DeZure AD, Stanley DA, Coates EE, Novik L, Enama ME, et al. Chimpanzee Adenovirus Vector Ebola Vaccine. *N Engl J Med.* 2017;376(10):928-38.
13. Martin JE, Sullivan NJ, Enama ME, Gordon IJ, Roederer M, Koup RA, et al. A DNA vaccine for Ebola virus is safe and immunogenic in a phase I clinical trial. *Clin Vaccine Immunol.* 2006;13(11):1267-77.
14. Kibuuka H, Berkowitz NM, Millard M, Enama ME, Tindikahwa A, Sekiziyu AB, et al. Safety and immunogenicity of Ebola virus and Marburg virus glycoprotein DNA vaccines assessed separately and concomitantly in healthy Ugandan adults: a phase 1b, randomised, double-blind, placebo-controlled clinical trial. *Lancet.* 2015;385(9977):1545-54.
15. Sarwar UN, Costner P, Enama ME, Berkowitz N, Hu Z, Hendel CS, et al. Safety and immunogenicity of DNA vaccines encoding Ebolavirus and Marburgvirus wild-type glycoproteins in a phase I clinical trial. *J Infect Dis.* 2015;211(4):549-57.
16. Dolzhikova IV, Zubkova OV, Tukhvatulin AI, Dzharullaeva AS, Tukhvatulina NM, Shcheblyakov DV, et al. Safety and immunogenicity of GamEvac-Combi, a heterologous VSV- and Ad5-vectored Ebola vaccine: An open phase I/II trial in healthy adults in Russia. *Hum Vaccin Immunother.* 2017:1-8.
17. Agnandji ST, Huttner A, Zinser ME, Njuguna P, Dahlke C, Fernandes JF, et al. Phase 1 Trials of rVSV Ebola Vaccine in Africa and Europe. *N Engl J Med.* 2016;374(17):1647-60.
18. Huttner A, Dayer JA, Yerly S, Combesure C, Auderset F, Desmeules J, et al. The effect of dose on the safety and immunogenicity of the VSV Ebola candidate vaccine: a randomised double-blind, placebo-controlled phase 1/2 trial. *Lancet Infect Dis.* 2015;15(10):1156-66.
19. Regules JA, Beigel JH, Paolino KM, Voell J, Castellano AR, Munoz P, et al. A Recombinant Vesicular Stomatitis Virus Ebola Vaccine - Preliminary Report. *N Engl J Med.* 2015.
20. Regules JA, Beigel JH, Paolino KM, Voell J, Castellano AR, Hu Z, et al. A Recombinant Vesicular Stomatitis Virus Ebola Vaccine. *N Engl J Med.* 2017;376(4):330-41.
21. Ebola ça suffit ring vaccination trial consortium. The ring vaccination trial: a novel cluster randomised controlled trial design to evaluate vaccine efficacy and effectiveness during outbreaks, with special reference to Ebola. *Bmj.* 2015;351:h3740.
22. Henao-Restrepo AM, Longini IM, Egger M, Dean NE, Edmunds WJ, Camacho A, et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. *Lancet.* 2015;386(9996):857-66.

23. Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ca Suffit!). *Lancet*. 2017;389:505-18.
24. Soumah A, for Study Team. Safety and immunogenicity of a vaccine against Ebola among frontline workers—Guinea, 4–7, 2015. Presented at 2016 Scientific Day of Epicentre and Médecins Sans Frontières held on 2nd June 2016 in Paris, France. 2016 Scientific Day of Epicentre and Médecins Sans Frontières; 02/06/2016; Paris, France 2016. p. 23.
25. Widdowson MA, Schrag SJ, Carter RJ, Carr W, Legard-Williams J, Gibson L, et al. Implementing an Ebola Vaccine Study - Sierra Leone. *MMWR Suppl*. 2016;65(3):98-106.
26. Goldstein S, Samai M, Fofanah A. The Sierra Leone Trial to Introduce a Vaccine Against Ebola (STRIVE): Evolution of a clinical trial during an Ebola outbreak. *Open Forum Infect Dis*. 2016;3 Suppl 1:S68.
27. Gunther S, Feldmann H, Geisbert TW, Hensley LE, Rollin PE, Nichol ST, et al. Management of accidental exposure to Ebola virus in the biosafety level 4 laboratory, Hamburg, Germany. *J Infect Dis*. 2011;204 Suppl 3:S785-90.
28. Lai L, Davey R, Beck A, Xu Y, Suffredini AF, Palmore T, et al. Emergency postexposure vaccination with vesicular stomatitis virus-vectored Ebola vaccine after needlestick. *Jama*. 2015;313(12):1249-55.
29. Matassov D, Mire C, Price J, et al. Phase 1 safety and immunogenicity of an attenuated VesiculoVax™ vectored EBOV vaccine. Abstract presented at the 8th International Symposium on Filoviruses held on 12–15 September 2016 in Antwerp, Belgium. 8th International Symposium on Filoviruses; 12–15/09/2016; Antwerp, Belgium 2016.
30. Kennedy SB, Neaton JD, Lane HC, Kieh MW, Massaquoi MB, Touchette NA, et al. Implementation of an Ebola virus disease vaccine clinical trial during the Ebola epidemic in Liberia: Design, procedures, and challenges. *Clin Trials*. 2016;13(1):49-56.
31. Bolay F. A randomized controlled trial of the safety and immunogenicity of two Ebola vaccines. Conference abstract (76LB) presented at Conference on Retroviruses and Opportunistic Infections (CROI) held on 22 – 25 February 2016 in Boston, USA. . 2016.



Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!)

Ana Maria Henao-Restrepo, Anton Camacho, Ira M Longini, Conall H Watson, W John Edmunds, Matthias Egger, Miles W Carroll, Natalie E Dean, Ibrahima Diatta, Moussa Doumbia, Bertrand Draguez, Sophie Duraffour, Godwin Enwere, Rebecca Grais, Stephan Gunther, Pierre-Stéphane Gsell, Stefanie Hossmann, Sara Viksmoen Watle, Mandy Kader Kondé, Sakoba Kéita, Souleymane Kone, Eewa Kuisma, Myron M Levine, Sema Mandal, Thomas Maugét, Gunnstein Norheim, Ximena Riveros, Aboubacar Soumah, Sven Trelle, Andrea S Vicari, John-Arne Rottingen*, Marie-Paule Kieny*



Summary

Background rVSV-ZEBOV is a recombinant, replication competent vesicular stomatitis virus-based candidate vaccine expressing a surface glycoprotein of Zaire Ebolavirus. We tested the effect of rVSV-ZEBOV in preventing Ebola virus disease in contacts and contacts of contacts of recently confirmed cases in Guinea, west Africa.

Methods We did an open-label, cluster-randomised ring vaccination trial (Ebola ça Suffit!) in the communities of Conakry and eight surrounding prefectures in the Basse-Guinée region of Guinea, and in Tomkolili and Bombali in Sierra Leone. We assessed the efficacy of a single intramuscular dose of rVSV-ZEBOV (2×10^7 plaque-forming units administered in the deltoid muscle) in the prevention of laboratory confirmed Ebola virus disease. After confirmation of a case of Ebola virus disease, we definitively enumerated on a list a ring (cluster) of all their contacts and contacts of contacts including named contacts and contacts of contacts who were absent at the time of the trial team visit. The list was archived, then we randomly assigned clusters (1:1) to either immediate vaccination or delayed vaccination (21 days later) of all eligible individuals (eg, those aged ≥ 18 years and not pregnant, breastfeeding, or severely ill). An independent statistician generated the assignment sequence using block randomisation with randomly varying blocks, stratified by location (urban vs rural) and size of rings (≤ 20 individuals vs > 20 individuals). Ebola response teams and laboratory workers were unaware of assignments. After a recommendation by an independent data and safety monitoring board, randomisation was stopped and immediate vaccination was also offered to children aged 6–17 years and all identified rings. The prespecified primary outcome was a laboratory confirmed case of Ebola virus disease with onset 10 days or more from randomisation. The primary analysis compared the incidence of Ebola virus disease in eligible and vaccinated individuals assigned to immediate vaccination versus eligible contacts and contacts of contacts assigned to delayed vaccination. This trial is registered with the Pan African Clinical Trials Registry, number PACTR201503001057193.

Findings In the randomised part of the trial we identified 4539 contacts and contacts of contacts in 51 clusters randomly assigned to immediate vaccination (of whom 3232 were eligible, 2151 consented, and 2119 were immediately vaccinated) and 4557 contacts and contacts of contacts in 47 clusters randomly assigned to delayed vaccination (of whom 3096 were eligible, 2539 consented, and 2041 were vaccinated 21 days after randomisation). No cases of Ebola virus disease occurred 10 days or more after randomisation among randomly assigned contacts and contacts of contacts vaccinated in immediate clusters versus 16 cases (7 clusters affected) among all eligible individuals in delayed clusters. Vaccine efficacy was 100% (95% CI 68.9–100.0, $p=0.0045$), and the calculated intraclass correlation coefficient was 0.035. Additionally, we defined 19 non-randomised clusters in which we enumerated 2745 contacts and contacts of contacts, 2006 of whom were eligible and 1677 were immediately vaccinated, including 194 children. The evidence from all 117 clusters showed that no cases of Ebola virus disease occurred 10 days or more after randomisation among all immediately vaccinated contacts and contacts of contacts versus 23 cases (11 clusters affected) among all eligible contacts and contacts of contacts in delayed plus all eligible contacts and contacts of contacts never vaccinated in immediate clusters. The estimated vaccine efficacy here was 100% (95% CI 79.3–100.0, $p=0.0033$). 52% of contacts and contacts of contacts assigned to immediate vaccination and in non-randomised clusters received the vaccine immediately; vaccination protected both vaccinated and unvaccinated people in those clusters. 5837 individuals in total received the vaccine (5643 adults and 194 children), and all vaccinees were followed up for 84 days. 3149 (53.9%) of 5837 individuals reported at least one adverse event in the 14 days after vaccination; these were typically mild (87.5% of all 7211 adverse events). Headache (1832 [25.4%]), fatigue (1361 [18.9%]), and muscle pain (942 [13.1%]) were the most commonly reported adverse events in this period across all age groups. 80 serious adverse events were identified, of which two were judged to be

Lancet 2017; 389: 505–18

Published Online
December 22, 2016
[http://dx.doi.org/10.1016/S0140-6736\(16\)32621-6](http://dx.doi.org/10.1016/S0140-6736(16)32621-6)

This online publication has been corrected. The first corrected version appeared at thelancet.com on December 23, 2016. The second corrected version appeared on February 2, 2017

See [Comment](#) page 479

*Contributed equally

WHO, Geneva, Switzerland (A M Henao-Restrepo MD, M Doumbia MD, G Enwere FWACP, P-S Gsell PhD, S Kone MSc, T Maugét MBA, X Riveros MSc, A S Vicari PhD, M-P Kieny PhD); Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK (A Camacho PhD, C H Watson MFPH, Prof W J Edmunds PhD); Department of Biostatistics, University of Florida, Gainesville, FL, USA (Prof I M Longini PhD, N E Dean PhD); Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland (Prof M Egger PhD); Centre for Infectious Disease Epidemiology and Research, University of Cape Town, Cape Town, South Africa (Prof M Egger); Public Health England, London, UK (M W Carroll PhD, S Mandal MD); Centre National d'Appui à la Lutte contre la Maladie, Bamako, Mali (M Doumbia); Médecins Sans Frontières, Brussels, Belgium (B Draguez MD); Bernard Nocht Institute for Tropical Medicine, University of Hamburg, Hamburg, Germany

(S Duraffour PhD, S Gunther MD, E Kuisma PhD); Epicentre, Paris, France (R Grais PhD, A Soumah MD); Clinical Trials Unit Bern, University of Bern, Bern, Switzerland (I Diatta MSc, S Hossmann MSc, S Trelle MD); Center Of Excellence For Training, Research On Malaria & Priority Diseases In Guinea, Conakry, Guinea (Prof M K Kondé PhD); Ebola Response, Ministry of Health, Conakry, Guinea (S Kéita MD); Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD, USA (Prof M M Levine MD); Division of Infectious Disease Control, Norwegian Institute of Public Health, Oslo, Norway (SV Watle MD, G Norheim PhD, Prof J-A Rottingen MD); Department of Health and Society, University of Oslo, Norway (Prof J-A Rottingen); Department of Global Health and Population, Harvard TH Chan School of Public Health, Boston, MA, USA (Prof J-A Rottingen) and Coalition for Epidemic Preparedness Innovations, care of Norwegian Institute of Public Health, Oslo, Norway (Prof J-A Rottingen)

Correspondence to: Dr Ana Maria Henao-Restrepo, World Health Organization, 1211 Geneva 27, Switzerland henaoestrepo@who.int

related to vaccination (one febrile reaction and one anaphylaxis) and one possibly related (influenza-like illness); all three recovered without sequelae.

Interpretation The results add weight to the interim assessment that rVSV-ZEBOV offers substantial protection against Ebola virus disease, with no cases among vaccinated individuals from day 10 after vaccination in both randomised and non-randomised clusters.

Funding WHO, UK Wellcome Trust, the UK Government through the Department of International Development, Médecins Sans Frontières, Norwegian Ministry of Foreign Affairs (through the Research Council of Norway's GLOBVAC programme), and the Canadian Government (through the Public Health Agency of Canada, Canadian Institutes of Health Research, International Development Research Centre and Department of Foreign Affairs, Trade and Development).

Copyright © 2016. World Health Organization. Published by Elsevier Ltd/Inc/BV. All rights reserved.

Introduction

Since the Ebola virus was first identified in 1976, sporadic outbreaks of Ebola virus disease have been reported in Africa, each causing high mortality.¹ No vaccine is currently licensed for preventing Ebola virus disease or other filovirus infections. The 2013–16 outbreak of Ebola virus disease in west Africa² highlighted the need to produce and assess a safe and effective Ebola vaccine for human beings.³ One promising vaccine candidate,⁴ the recombinant, replication-competent, vesicular stomatitis virus-based vaccine expressing the glycoprotein of a Zaire Ebolavirus (rVSV-ZEBOV), is protective in challenge models in several animal species,^{5–16} including mice, hamsters, guinea pigs, and non-human primates.^{4,5} A single dose completely protected non-human primates against high-dose challenge (around 1000 particle-

forming units) when administered between 7 and 31 days pre-challenge^{2–9} and partly protected non-human primates when administered from 3 days before⁷ to 24 h after challenge with the Makona strain responsible for the west African epidemic.¹¹

We therefore undertook Ebola ça Suffit! (translated as “Ebola that’s enough!”), a ring vaccination phase 3 efficacy trial in Guinea whose primary objective was to assess the efficacy of the rVSV-ZEBOV vaccine for the prevention of Ebola virus disease in human beings (the ring vaccination approach was inspired by the surveillance-containment strategy that led to smallpox eradication).¹⁷ Preliminary results indicated 100% vaccine efficacy (95% CI 74.7–100.0) at interim analysis, after which the delayed-vaccination arm was discontinued.¹⁸ Here, we present the final results of the trial.

Research in context

Evidence before this study

There are currently no licensed vaccines for preventing Ebola virus disease or other filovirus infections. The rVSV-ZEBOV candidate vaccine has been reported to be protective in challenge models in several non-human species. We searched Medline and EMBASE without language restrictions for articles published from January, 1990, to July 20, 2015, to identify any published phase 3 clinical trials assessing the efficacy of Ebola vaccines, using the search terms “Ebola virus”, “filovirus”, “prophylaxis”, “vaccine”, and “clinical trials”. The rVSV-ZEBOV vaccine has been studied in phase 1 and phase 2 studies, which have documented its immunogenicity and safety profile. To our knowledge, ours is the only phase 3 trial of this vaccine in west Africa that has reported results, and no trial until now has used the ring vaccination cluster-randomised design. Therefore, we could not do a detailed systematic review at this point in time.

Added value of this study

Ebola Ça Suffit used a novel trial design based on identification of people at risk around a newly confirmed case of Ebola virus disease (contacts and contacts of contacts) and ring vaccination to improve the prospect of generating robust evidence on the effects of the vaccine despite the low and decreasing incidence

of Ebola virus disease. Individuals were either randomly assigned to immediate vaccination or delayed vaccination, or not randomly assigned (and received immediate vaccination). Interim analysis suggested that rVSV-ZEBOV offered very high protection, leading to the delayed-vaccination arm being discontinued. Final data from all trial clusters (randomised and non-randomised, with children included in the non-randomised group) showed that at 10 days or more after randomisation, there were no cases of Ebola virus disease among immediately vaccinated contacts and contacts of contacts; ie, 100% protection. Adverse events data indicated no safety concerns in adults or children.

Implications of all the available evidence

We used a novel trial design, which had a high probability of generating evidence on the individual and cluster-level effects of the vaccine despite the low and decreasing incidence of Ebola virus disease. These results indicate that rVSV-ZEBOV is safe and effective in averting Ebola virus disease when added to established control measures as a ring vaccination approach. Ring vaccination trials might have application in the assessment of other vaccine candidates in epidemics of other viral haemorrhagic fevers or other emerging infectious diseases.

Methods

Study design and participants

The Guinea ring vaccination trial was a cluster-randomised controlled trial designed to assess the effect of one dose of the candidate vaccine in protecting against laboratory confirmed Ebola virus disease. We did this trial in the community in Conakry and eight surrounding prefectures in the Basse-Guinée region of Guinea (appendix).

The Guinean national medicines regulatory agency (Direction Nationale de la Pharmacie et du Laboratoire) and the national ethics committee (Comité National d'Éthique pour la Recherche en Santé), the WHO Ethical Research Committee, and Norwegian Regional Committees for Medical and Health Research Ethics approved the study protocol. In Aug, 2015, after approval by Sierra Leonean National Regulatory Authority and the Ethics Review Committee, the trial was extended to Sierra Leone (Tomkolili and Bombali).

Ebola virus spread across many geographical areas of Guinea, mainly through familial and social networks and funeral exposures.¹⁹ After confirmation of a case of Ebola virus disease (index case), we enumerated and randomised clusters (called rings) of epidemiologically linked people.²⁰ The ring vaccination design ensured that the study was undertaken in pockets of high incidence of Ebola virus disease despite the declining epidemic and an overall low attack rate (ie, the total number of cases of Ebola virus disease in the three worst affected countries divided by the estimated total population of these countries; estimated here as about 0·13%). Details of the study protocol, study team composition, study procedures, and statistical analysis plan have been previously reported.^{18,20}

Briefly, we enumerated clusters as a list of all contacts and contacts of contacts of the index case including residents temporarily absent at the time of enumeration. We defined contacts as individuals who lived in the same household, visited or were visited by the index case after the onset of symptoms, provided him or her with unprotected care, or prepared the body for the traditional funeral ceremony. These contacts included high-risk contacts who were in close physical contact with the patient's body or body fluids, linen, or clothes.²¹ Contacts of contacts were the neighbours of the index case to the nearest appropriate geographical boundary plus the household members of any high-risk contacts living away from the index cases' residence. A new cluster was defined if at least 60% of the contacts and contacts of contacts were not enumerated in a previous cluster.

We randomly assigned clusters into immediate vaccination or vaccination delayed by 21 days. Exclusion criteria were: history of Ebola virus disease (self-declared or laboratory confirmed), being aged less than 18 years, pregnancy (verbally declared) or breastfeeding (women were invited, but not forced, to take a pregnancy test), history of administration of other experimental

treatments during the past 28 days, history of anaphylaxis to a vaccine or vaccine component, or serious disease requiring confining to bed or admission to hospital by the time of vaccination. Within each cluster, all people who were eligible and consented were offered vaccination.

A team obtained written informed consent from all eligible contacts and contacts of contacts using a printed information sheet. If the person in question was illiterate, these documents were read to him or her in their local language and a fingerprint from the participant and the signature of an independent literate witness documented consent. Eligible contacts and contacts of contacts were informed of the outcome of the randomisation at the end of the informed consent process.

The trial personnel were predominantly composed of nationals from Guinea and other African countries. An internal quality assurance and quality control system was put in place, with 100% monitoring of study documents. An independent data and safety monitoring board (DSMB) reviewed the study protocol and the analysis plan before the analysis and assessed adverse events and efficacy results. The pilot phase of the trial began on March 23, 2015, and random assignment of clusters started on April 1, 2015. On July 31, 2015, random assignment into immediate and delayed vaccination was discontinued on the recommendation of the DSMB, whose decision took into consideration the interim analysis showing 100% vaccine efficacy¹⁸ (although they noted that the prespecified α spending criterion of 0·0027 was not achieved) and the low probability of being able to recruit substantial numbers of additional rings (given the declining number of cases of Ebola virus disease in the country). Thereafter, all identified rings received immediate vaccination. Ring enrolment was concluded on Jan 20, 2016.

Additionally, in view of emerging data for vaccine safety among children aged 6–17 years,²² the protocol was amended on Aug 15, 2015, to also include children in this age group. Consequently, we obtained written informed consent from the parents or guardians of children aged 6–17 years with written assent from children aged 12–17 years.

Randomisation and masking

Contacts and contacts of contacts of individuals with Ebola virus disease were enumerated into clusters (and the information stored on a list) and these clusters were cluster-randomised (1:1) to either immediate vaccination or delayed vaccination (21 days later) of all eligible individuals.²⁰ The teams who defined the clusters were different from the team who took informed consent or did the vaccinations. Randomisation took place only after the list enumerating all the contacts and contacts of contacts of a cluster was closed. An independent statistician not otherwise involved in the trial generated the allocation sequence, and Ebola response teams and laboratory workers were unaware of the allocation of clusters.

We used block randomisation randomly varying block sizes, stratified by location (urban *vs* rural) and size of rings (≤ 20 *vs* > 20 individuals). The randomisation list was stored in a data management system not accessible to anyone involved in the recruitment of trial participants. Allocation of a cluster was done once the enumeration of the cluster (ie, the list of contacts and contacts of contacts) was done. Allocation of the cluster was informed to the participants at the end of the informed consent process. In the pilot phase and after July 27, 2015, clusters were not randomised and all eligible participants received the vaccine immediately after informed consent.

Procedures

Active surveillance for, and laboratory confirmation of, cases of Ebola virus disease were independently undertaken by the national surveillance system, and cases of Ebola virus disease were confirmed by designated surveillance laboratories.^{23,24} The national Ebola surveillance team and the trial team were independent; the trial team did not communicate any specific information to the surveillance teams and laboratories about which cases of Ebola virus disease were used to form a new cluster or which people would be included in a cluster.

Within 1–2 days of confirmation of a new case of Ebola virus disease, our social communication teams visited the area of residence of the case and sought the communities' consent for the trial team to enumerate a new cluster. A second team enumerated the cluster list of contacts and contacts of contacts. This list was then stored. From the complete cluster list, preliminary inclusion and exclusion criteria were applied (eg, age) to generate a list of all potential trial participants (eligible contacts and contacts of contacts) to be approached for consent. Eligible contacts and contacts of contacts cluster-randomised to immediate vaccination had only one opportunity to give their informed consent; ie, during the first contact (day 0). Eligible contacts and contacts of contacts assigned to delayed clusters had two opportunities to consent: day 0 and day 21 when vaccination was offered to the cluster.

The rVSV-ZEBOV vaccine (Merck Sharp & Dohme, Kenilworth, NJ, USA) was selected for the trial according to a framework developed by an independent group of experts.²⁵ All vaccinees received one dose of 2×10^7 plaque-forming units of the rVSV-ZEBOV vaccine intramuscularly in the deltoid muscle.

To assess safety, vaccinees were observed for 30 min post-vaccination and at home visits on days 3, 14, 21, 42, 63, and 84. The possible causal relationship of any adverse event to vaccination was judged by the study physicians and reported to the DSMB. Vaccinees were provided with acetaminophen or ibuprofen for the management or prevention of post-vaccination fever.

Outcomes

The primary outcome was a laboratory confirmed case of Ebola virus disease, defined as any probable or suspected case from whom a blood sample was taken and laboratory confirmed as positive for Ebola virus; or any deceased individual with probable Ebola virus disease, from whom a post-mortem sample taken within 48 h after death was laboratory confirmed as positive for Ebola virus disease.^{23,24} In our secondary objectives, we analysed the vaccine effect on deaths due to Ebola virus disease. A prespecified secondary analysis examined the overall ring vaccination effectiveness in protecting all contacts and contacts of contacts in the randomised clusters (including unvaccinated cluster members) although the trial was not powered to measure population level effects.

Local laboratories of the Ebola surveillance system confirmed cases by either detection of virus RNA by reverse transcriptase-PCR or detection of IgM antibodies directed against Ebola virus.^{23,24} If available to us, aliquots of samples were retested at the European Mobile Laboratory using the RealStar Zaire Ebolavirus reverse transcriptase-PCR kit 1.0. All index cases and secondary cases of Ebola virus disease occurring in the clusters were documented using laboratory results, case investigation forms and information on chains of transmission developed independently by the national surveillance team and, if needed, supplemented with information collected by trial personnel.

A priori, we defined that only cases of Ebola virus disease with an onset 10 or more days from randomisation were valid outcomes for the trial.^{18,20} This was done to account for the incubation period of Ebola virus disease,^{26,27} the time between onset of symptoms and laboratory confirmation and the unknown period between vaccination and a vaccine-induced protective immune response (lag period).²⁰ Additionally, vaccinated cases of Ebola virus disease with an onset of more than 31 days after random assignment were censored to account for vaccination in the delayed clusters on day 21.^{18,20}

Statistical analysis

The sample size calculation is described elsewhere.^{18,20} We analysed outcomes at the cluster level rather than individual level using the cumulative incidence of valid outcomes for each cluster. Additional to the planned analyses,²⁰ and to address external suggestions on our interim analysis report^{28–30} we did further analyses of the randomised data. For the randomised evidence, we compared the incidence of Ebola virus disease in: 1) all vaccinated in immediate versus all contacts and contacts of contacts eligible and who consented on day 0 visit in delayed; 2) all vaccinated in immediate versus all contacts and contacts of contacts eligible in delayed; 3) all contacts and contacts of contacts eligible in immediate versus all contacts and contacts of contacts eligible in delayed; and 4) all contacts and contacts of contacts in immediate versus all contacts and contacts of contacts in delayed.

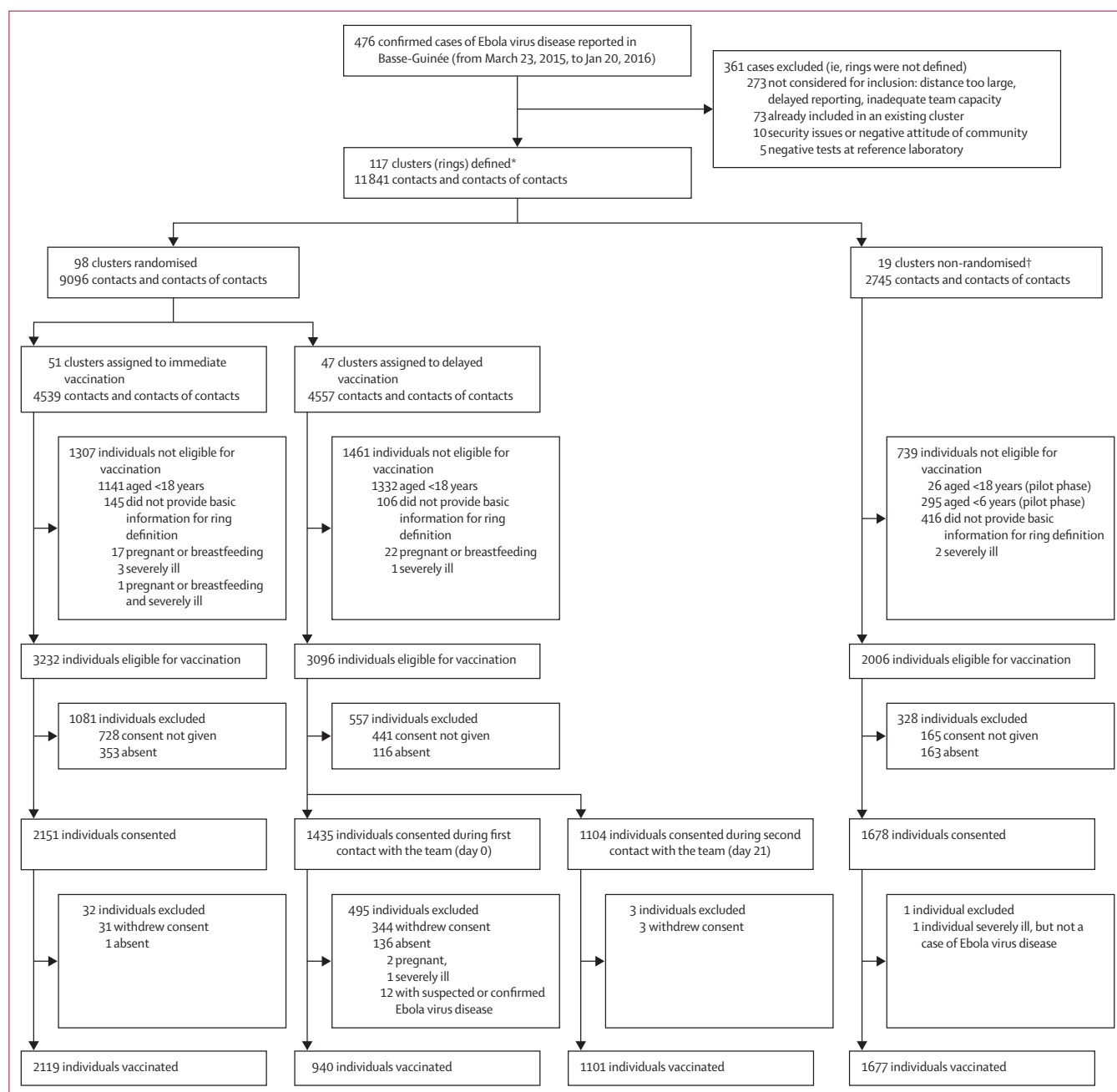


Figure 1: Trial profile

The vaccine effects analyses set included all eligible contacts and contacts of contacts and the safety analysis set included all participants who had received the vaccine. Participants were analysed in the group corresponding to the allocated arm. *Including two non-randomised rings from Sierra Leone with 325 contacts and 255 contacts of contacts. †Including three pilot rings.

We also analysed the evidence from all clusters, including data from randomised and non-randomised clusters. For all clusters, we compared the incidence of Ebola virus disease in: all vaccinated in immediate versus all contacts and contacts of contacts who were eligible in delayed plus all contacts and contacts of contacts who were eligible but never

vaccinated in immediate; all contacts and contacts of contacts in immediate versus all contacts and contacts of contacts in delayed and; all vaccinated in immediate versus all eligible but never vaccinated in immediate. Additionally, we characterised the risk of Ebola exposure and participant characteristics for all the groups being compared.

	Randomised		Not randomised	
	Assigned to immediate vaccination (51 clusters)	Assigned to delayed vaccination (47 clusters)	Assigned to immediate vaccination (19 clusters)	All clusters (117 clusters)
Index cases used to define clusters				
Age (years)	35 (18–43)	35 (27–50)	23 (13–42)	35 (20–47)
Women	27/51 (53%)	31/47 (66%)	12/19 (63%)	70/117 (60%)
Dead at time of randomisation	30/51 (59%)	32/47 (68%)	9/19 (47%)	71/117 (61%)
Time from onset of symptoms to admission to hospitalisation or isolation (days)	3.9 (2.9)	3.8 (2.6)	3.2 (2.4)	3.7 (2.7)
Time from onset of symptoms for index cases to randomisation of cluster (days)	9.7 (5.3)	11 (4.1)	..	10.3 (4.8)
Time from onset of symptoms for index cases to inclusion of cluster (days)	9.8 (5.1)	10.9 (4.1)	7.3 (3.7)	9.9 (4.6)
Characteristics of clusters				
Located in rural areas	39/51 (76%)	36/47 (77%)	9/19 (47%)	84/117 (72%)
Total number of people in cluster	80 (64–101)	81 (69–118)	105 (49–185)	83 (66–115)
Data are median (IQR), n/N (%), or mean (SD). ..=not applicable.				

Table 1: Baseline characteristics of clusters and index cases

See Online for appendix

Similar to the interim analysis, if no cases of Ebola virus disease occurred in one group, we derived a 95% CI for the vaccine effect by fitting a β -binomial distribution to the cluster-level numerators and denominators and used an inverted likelihood ratio test to identify the lower bound for vaccine effect. For comparisons in which cases of Ebola virus disease occurred in both groups, we fitted a Cox proportional hazards model using a cluster-level frailty term to adjust for clustering within rings.¹⁸ We used Fisher's exact test to compare the proportions of clusters with at least one event across the two trial groups. The primary analysis was per protocol. We did all analyses in R, version 3.3.1.³¹ We received comments on the protocol and statistical analysis plan from an independent scientific advisory group. Independent clinical monitors validated 100% of the case report forms and an independent auditor assessed the study site, field activities, and supporting documentation. This trial is registered with the Pan African Clinical Trials Registry, number PACTR201503001057193.

Role of the funding source

Funders other than the institutions of the authors had no role in the design of the study, data collection, data analysis, data interpretation, or writing of the report. The authors contributed to study design and data interpretation. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

During the trial period between March 23, 2015, and Jan 20, 2016, there were 476 cases of Ebola virus disease

in Guinea, all in the study area. 117 were index cases for clusters, 27 were index cases and also endpoints. In total, 105 were endpoints (75 among the eligible contacts and contacts of contacts and 30 among non-eligible contacts and contacts of contacts). We did not define a cluster around 281 (59%) of the cases of Ebola virus disease occurring during this period. These 281 cases of Ebola virus disease mostly arose during March and April, 2015, during the pilot phase and when most study teams were still being trained and the study did not have full capacity (figure 1; appendix).

In all, we obtained aliquots from 79% (93/117) Ebola virus disease index cases; 88% (30/34) of confirmed Ebola virus disease outcome cases with onset 10 or more days after randomisation and 80% (57/71) of all confirmed Ebola virus disease outcome cases. 5837 individuals in total received the vaccine (5643 adults and 194 children); all were followed up for 84 days.

The measured characteristics of index cases of Ebola virus disease and clusters were broadly comparable at baseline for immediate, delayed, and non-randomised clusters, including time from onset to randomisation and the proportion of index cases who were dead at the time of randomisation (table 1). Mean time from symptom onset in index cases to ring inclusion was 9.8 days in immediate rings, 10.9 days in delayed rings, and 7.3 days in non-randomised rings. Randomised clusters had a median 80 people (IQR 64–101) for immediate and a median 81 people (69–118) for delayed clusters. Non-randomised clusters were slightly larger with a median 105 people (49–185), partly due to public knowledge of the interim results as well as to the eligibility extension to children aged 6 years and older.

At baseline, the characteristics of contacts and contacts of contacts in all comparator groups for immediate, delayed and non-randomised clusters were largely comparable (table 2; appendix). A higher fraction of high-risk contacts was included in the immediate clusters. More than 80% of contacts and contacts of contacts were defined as contacts of contacts. Compliance with follow-up visits on all types of clusters and for all scheduled visits was more than 80% with no differences between groups (appendix).

In the randomised part of the trial, there were 4539 contacts and contacts of contacts in 51 clusters in the immediate vaccination arm (of whom 3232 were eligible, 2151 consented, and 2119 were immediately vaccinated) and 4557 contacts and contacts of contacts in 47 clusters in the delayed vaccination arm (of whom 3096 were eligible, 2539 consented and 2041 were vaccinated 21 days after randomisation; figure 1). In immediate clusters, 34% (1113/3232) of eligible individuals were not vaccinated mainly because informed consent was not obtained (n=728) or it was withdrawn (n=32), or because individuals were absent at the time of the team's visit (n=353; figure 1, tables 1, 2; appendix). In delayed clusters, 34% (1055/3096) of eligible individuals

were not vaccinated mainly because informed consent was not obtained or it was withdrawn (n=788) or because individuals were absent at the time of the team's visit (n=252) or developed Ebola virus disease during the 0–20 days period (n=12; figure 1, tables 1, 2; appendix). Additionally, two individuals were pregnant, and one was severely ill, so these were not vaccinated. Among those who consented in the delayed clusters, 57% (1435/2539) gave their consent during the first visit with the study team (day 0) and 43% (1104/2539) gave consent on the vaccination visit (day 21); all were included in the cluster enumeration list.

Random assignment had little effect on the onset of Ebola virus disease during days 0–9. 20 cases of Ebola virus disease occurred among 3232 eligible contacts and contacts of contacts (nine clusters affected) in 51 immediate clusters versus 21 cases among 3096 eligible contacts and contacts of contacts (14 clusters affected) in 47 delayed clusters (table 3; appendix). However, vaccine allocation reduced Ebola virus disease onset to 0 cases from 10 days post-randomisation in immediately vaccinated contacts and contacts of contacts versus ten cases of Ebola virus disease (four clusters affected) among the eligible contacts and contacts of contacts in delayed clusters who gave consent on day 0. Vaccine efficacy was still 100% (table 3). The calculated intraclass coefficient (ICC) was high at 0.14, largely due to clustering of six confirmed endpoint cases of Ebola virus disease in one of the clusters. This would make the Fisher's test even more conservative. This ICC value contrasts with the ICC value of 0.05²⁰ that we used to estimate the trial sample size and power calculation (appendix).

One additional case of Ebola virus disease was identified in the delayed clusters among eligible contacts and contacts of contacts who consented on day 21 for a total of 11 cases of Ebola virus disease among eligible and consenting contacts and contacts of contacts in delayed clusters. The remaining ten cases in the delayed clusters were among the eligible contacts and contacts of contacts who consented on day 0. Among these 11 cases of Ebola virus disease, including four vaccinees (onset 0, 2, 6, and 6 days after vaccination), seven (64%) were among unvaccinated contacts (one high-risk contact) and the four others were contacts of contacts (appendix).

The overall ring vaccination effectiveness in protecting all contacts and contacts of contacts in the randomised clusters (including unvaccinated cluster members) was 64.6% (table 3), with 65.6% of the eligible contacts and contacts of contacts receiving the vaccine at the cluster level.

No cases of Ebola virus disease occurred 10 days or more after randomisation among randomly assigned contacts and contacts of contacts vaccinated in immediate clusters versus 16 cases (7 clusters affected) among all eligible individuals in delayed clusters (table 3). Vaccine efficacy was 100% (95% CI 68.9–100.0, p=0.0045), and the calculated ICC was 0.035. Additionally, we

	Randomly assigned		Not randomly assigned*				Totality of evidence	
	Assigned to immediate vaccination (51 clusters, n=3232)		Assigned to delayed vaccination (47 clusters, n=3096)		Assigned to immediate vaccination (19 clusters, n=2006)		All clusters (117 clusters, n=8334)	
	Consent	No consent	Consent visit day 0†	Consent visit day 21‡	Consent	No consent	Immediately vaccinated	Delayed or never vaccinated
Individuals' characteristics								
Number of individuals	2151	1081	1435	1104	1678	328	3796	4538
Age (years)	40 (29–55)	30 (25–45)	39 (27–53)	37 (27–50)	30 (22–44)	25 (18–35)	35 (25–50)	35 (25–50)
Women	640/2151 (30%)	608/1081 (56%)	428/1434 (30%)	404/1104 (37%)	593/1678 (35%)	179/328 (54.6%)	1223/3796 (32%)	1948/4537 (43%)
Contacts with index cases								
No detailed contact information (no consent)	0/2151	1081/1081 (100%)	0/1435	0/1104	0/1678	328/328 (100%)	0/3796	1966/4538 (43%)
Contact of contact‡	1727/2151 (80%)	..	1160/1435 (81%)	971/1104 (88%)	1418/1678 (85%)	..	3116/3796 (82%)	2160/2572 (84%)
Contact‡	424/2151 (20%)	..	275/1435 (19%)	133/1104 (12%)	260/1678 (15%)	..	680/3796 (18%)	412/2572 (16%)
High-risk contact‡	330/2151 (15%)	..	171/1435 (12%)	58/1104 (5%)	246/1678 (15%)	..	574/3796 (15%)	231/2572 (9%)

Data are median (IQR) or n/N (%). ..data not available. †Six non-randomised rings included children aged 6 years and older (n=273). ‡Informed consent was obtained either during the first visit (day 0) or the second visit (day 21) of the trial team. ‡Proportion calculated among individuals with available contact information. ‡Two individuals were pregnant and one was severely ill.

Table 2: Baseline characteristics of eligible contacts and contacts of contacts

	All clusters*				Randomised clusters†			
	1	2	3	4	5	6	7	8
	All vaccinated in immediate (group A) vs all contacts and contacts of contacts in delayed plus all never-vaccinated in immediate or non-randomised (group B)	All vaccinated in immediate (group A) vs all eligible in delayed plus all eligible never-vaccinated in immediate (group B)	All contacts and contacts of contacts in immediate (group A) vs delayed (group B)	All vaccinated in immediate (group A) vs all eligible never vaccinated in immediate (group B)	All vaccinated in immediate (group A) vs all eligible and consented on day 0 visit in delayed (group B)	All vaccinated in immediate (group A) vs all eligible in delayed (group B)	All eligible in immediate (group A) vs all eligible delayed (group B)	All contacts and contacts of contacts in immediate (group A) vs all contacts and contacts of contacts in delayed (group B)
Group A								
Number of individuals (clusters)	3775 (70)	3775 (70)	7241 (70)	3775 (70)	2108 (51)	2108 (51)	3212 (51)	4513 (51)
Cases of Ebola virus disease (clusters affected)	0 (0)	0 (0)	12 (7)	0 (0)	0 (0)	0 (0)	7 (4)	10 (5)
Attack rate	0%	0%	0.17%	0%	0%	0%	0.22%	0.22%
Group B								
Number of individuals (clusters)	7995 (116)	4507 (104)	4529 (47)	1432 (57)	1429 (46)	3075 (47)	3075 (47)	4529 (47)
Cases of Ebola virus disease (clusters affected)	34 (15)	23 (11)	22 (8)	7 (4)	10 (4)	16 (7)	16 (7)	22 (8)
Attack rate	0.43%	0.51%	0.49%	0.49%	0.7%	0.52%	0.52%	0.49%
Vaccine effect								
Vaccine efficacy/ effectiveness‡ (%; 95% CI)	100% (77.0 to 100.0)	100% (79.3 to 100.0)	70.1% (-4.9 to 91.5)	100% (-51.5 to 100.0)	100% (63.5 to 100.0)	100% (68.9 to 100.0)	64.6% (-46.5 to 91.4)	64.6% (-44.2 to 91.3)
p value§	0.0012	0.0033	0.2759	0.125	0.0471	0.0045	0.344	0.3761

*Randomly assigned and non-randomly assigned individuals who were allocated to immediate vaccination were combined. †Non-randomised immediate clusters are excluded from this analysis. ‡From fitting a β -binomial distribution to the cluster-level numerators and denominators and using an inverted likelihood ratio test to identify the lower bound for vaccine efficacy (columns 1, 2, 5, and 6); from a Cox proportional hazards model (column 3, 7, and 8); from signed test (two-sided): probability of observing endpoints in control groups among treatment-control mismatched pairs and under the null hypothesis that the vaccine has no efficacy (column 4). §From Fisher's exact test (two-sided), which is approximate for columns 1 and 2. From signed test (two-sided): probability of observing endpoints in control groups among treatment-control mismatched pairs and under the null hypothesis that the vaccine has no efficacy (column 4).

Table 3: Effect of vaccine on cases of Ebola virus disease in different study populations

enumerated 2745 contacts and contacts of contacts (three in the pilot phase) in 19 non-randomised clusters, 2006 of whom were eligible and 1677 were immediately vaccinated, including 194 children aged 6–17 years (figure 1).

The evidence from all 117 clusters (randomised and non-randomised) showed that no cases of Ebola virus disease occurred 10 days or more after randomisation among the 3775 immediately vaccinated contacts and contacts of contacts versus 23 cases (11 clusters affected) among the 4507 eligible contacts and contacts of contacts in delayed plus all eligible contacts and contacts of contacts never vaccinated in immediate clusters (tables 3, 4; appendix). Of these 23 cases of Ebola virus disease, four were vaccinated but had onset of Ebola virus disease at days 0, 2, 6, and 6 after vaccination and the remaining 19 cases were among non-vaccinated contacts and contacts of contacts. Thus, immediate vaccination resulted in complete protection against subsequent onset of Ebola virus disease 10 days later or more. The estimated vaccine efficacy here was 100% (95% CI 79.3–100.0, $p=0.0033$; table 4). 52% of contacts and contacts of contacts assigned to immediate vaccination

and in non-randomised clusters received the vaccine immediately; vaccination protected both vaccinated and unvaccinated people in those clusters.

Cases occurred in the first 10 days after randomisation for all comparison groups, at similar times; there were no cases of Ebola virus disease among vaccinees from 10 days after randomisation or vaccination in any of the groups, with all cases arising in clusters more than 10 days post-vaccination occurring in unvaccinated individuals (figure 2). Additionally, the rVSV-ZEBOV vaccine seemed to have contributed to interrupt Ebola transmission in the clusters because no cases of Ebola virus disease among vaccinees or unvaccinated individuals were observed in immediate vaccinated clusters after 21 days after vaccination (figure 2). Details about the distribution of cases of Ebola virus disease among the various groups are in table 4 and the appendix.

Because no cases of Ebola virus disease occurred at 10 days or later in the vaccinated group, the vaccine effect was high for all the comparisons of vaccine effect on deaths due to Ebola virus disease (appendix), with 100% effect (95% CI 62.6–100, $p=0.0102$) when comparing all vaccinated in immediate clusters versus

	Eligible adults assigned to immediate vaccination		All eligible adults assigned to delayed vaccination	Eligible adults not assigned		Non-eligible* participants (not vaccinated)		
	Immediately Vaccinated	Never vaccinated		Immediately Vaccinated	Never vaccinated	All assigned to immediate vaccination	All assigned to delayed vaccination	All not assigned
Contacts and contacts of contacts (clusters)	2119 (51)	1113 (48)	3096 (47)	1677 (19)	329 (10)	1307 (50)	1461 (47)	739 (19)
Attack rates								
Overall	11/2119 (0.5%)	16/1113 (1.4%)	37/3096 (1.2%)	10/1677 (0.6%)	1/329 (0.3%)	9/1307 (0.7%)	13/1461 (0.9%)	8/739 (1.1%)
Onset <10 days since being randomly assigned	11/2111 (0.5%)	9/1113 (0.8%)	21/3096 (0.7%)	10/1677 (0.6%)	1/329 (0.3%)	6/1307 (0.5%)	7/1461 (0.5%)	6/739 (0.8%)
Onset ≥10 days since being randomly assigned	0/2108 (0.0%)	7/1104 (0.6%)	16/3075 (0.5%)	0/1667 (0.0%)	0/328 (0.0%)	3/1301 (0.2%)	6/1454 (0.4%)	2/733 (0.3%)
Clusters affected by cases with onset ≥10 days after being randomly assigned								
0 cases	51/51 (100%)	44/48 (91.7%)	40/47 (85.1%)	19/19 (100%)	10/10 (100%)	48/50 (96%)	44/47 (93.6%)	17/19 (89.5%)
1 case	..	2/48 (4.2%)	3/47 (6.4%)	1/50 (2%)	2/47 (4.3%)	2/19 (10.5%)
2 cases	..	1/48 (2.1%)	2/47 (4.3%)	1/50 (2%)
3 cases	..	1/48 (2.1%)	1/47 (2.1%)
4 cases	1/47 (2.1%)	..
6 cases	1/47 (2.1%)

*Aged <18 years, pregnant, or lactating (full list of exclusion criteria in references 19 and 20). ..=data not available.

Table 4: Distribution of confirmed cases of Ebola virus disease among enumerated contacts and contacts of contacts in all clusters

all eligible in delayed clusters. We were not able to do the planned secondary analyses on vaccine effect against probable and suspected cases because of near-universality of laboratory testing of such cases in Guinea during the study period, leaving only 26/502 (5%) of cases without a definitive diagnosis. Five cases of Ebola virus disease initially considered as index cases for clusters were negative by confirmatory retesting and the corresponding clusters were therefore excluded from the analysis. No endpoint cases tested negative on confirmatory retesting.

In total, we identified 105 cases of Ebola virus disease among all contacts and contacts of contacts (eligible or not for vaccination) in the 117 clusters defined (98 randomised clusters and 19 non-randomised clusters). The overall attack rate was 0.9% (95% CI 0.7–1.1) considering the 105 cases occurring among 11841 individuals enumerated in 117 rings. None of the cases occurred in vaccinated individuals 10 days or more after being vaccinated (figure 3; appendix).

Moreover, when comparing all contacts and contacts of contacts in clusters immediately vaccinated versus all contacts and contacts of contacts in delayed clusters plus all contacts and contacts of contacts never vaccinated in immediate or non-randomised clusters, vaccine protection

was 100% (table 3) further indicating that the vaccine is highly protective (table 4; appendix). This represents the totality of evidence for high vaccine efficacy when comparing all immediately vaccinated people to all delayed or unvaccinated people. The overall ring vaccination effectiveness in protecting all contacts and contacts of contacts (including vaccinated and unvaccinated cluster members) was 70.1% (table 3) with 52.1% (3796/7284) of the contacts and contacts of contacts vaccinated.

Cases occurred in the first 10 days at a similar time in immediate, delayed, and non-randomised clusters and all comparison groups. There were no cases of Ebola virus disease among vaccinees from 10 days post-vaccination in any of the groups (figure 3, appendix). Moreover, rVSV-ZEBOV vaccine contributed to interrupt Ebola transmission with no cases of Ebola virus disease after 32 days after randomisation in randomly assigned and non-randomly assigned clusters in vaccinated and non-vaccinated individuals (figure 2, 3).

3149 (53.9%) of 5837 individuals reported at least one adverse event in the 14 days after vaccination (appendix); across all adverse events, solicited and unsolicited, 87.5% (6311/7211) were mild, 11.0% (793/7211) moderate, and 1.2% (83/7211) severe (appendix). Across all age groups, headache (1832 [25.4%]), fatigue (1361 [18.9%]),

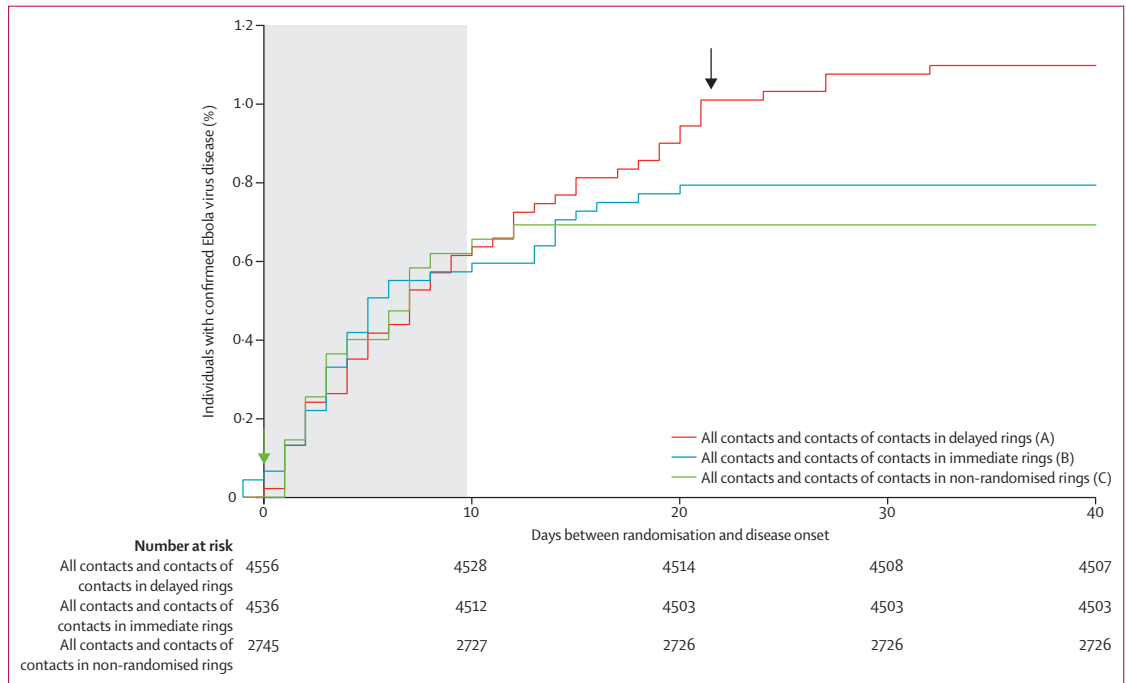


Figure 2: Kaplan-Meier plots for all confirmed cases of Ebola virus disease among all contacts and contacts of contacts in immediate, delayed, and non-randomised clusters

Arrows show time of vaccination (at day 0 or day 21). The shaded area denotes the a priori defined lag time of 0–9 days. *Individuals aged 6–18 years were eligible for immediate vaccination in non-pilot, non-randomised rings. Description of Ebola virus disease cases 10 days or more after randomisation: A (allocated to delayed vaccination): 22 cases; six were children (aged <18 years); one was eligible and did not consent; four were absent; 11 were eligible and consented, including seven eligible and consented with illness onset on days 10–20 after randomisation plus four eligible, consented, and delayed vaccinated with onset on days 21–30 after randomisation (0, 2, 6, and 6 days after their delayed vaccination). B: ten cases, all unvaccinated; two were children (aged <18 years); four were eligible and did not consent; three were absent; one was not eligible (ie, pregnant, breastfeeding, or severely ill). C: two cases, both were children (aged <6 years and hence unvaccinated).

and muscle pain (942 [13.1%]) were the most commonly reported adverse events in this period across all age groups. Data from children indicated that in the 3 days after vaccination, by percentage of individuals with the events, the commonly reported adverse events were headache (51/97 [52.6%]), fatigue (11/97 [11.3%]), and injection pain (9/97 [9.3%]). Adults most commonly reported headache (1781/7114 [25.0%]), fatigue (1350/7114 [19.0%]), and muscle pain (937/7114 [13.2%]) in the same period. Arthralgia was the fourth most reported adverse event (table 5; reported by 17.9% of vaccinated participants), and was reported in 4/180 (2.2%) of vaccinated children with a mean duration of 4.5 days (IQR 3–5) and in 915/4960 (18.5%) of vaccinated adults with a mean duration of 2 days (2–4). Cases resolved spontaneously without sequelae.

80 serious adverse events were reported. The most common diagnosis was Ebola virus disease in 39/80 participants (48.7%) followed by road traffic accident injury in 4/80 (5%; appendix). Two serious adverse events were judged to be related to vaccination (a febrile reaction and one anaphylaxis, which resolved without sequelae) and one possibly related (influenza-like illness) which also recovered without sequelae. 15 serious adverse events occurred among enrolled but

non-vaccinated participants; 14 were Ebola virus disease in participants (all with onset 0–10 days after randomisation) and one was a road traffic accident injury.

Discussion

The results presented in this final analysis of our Ebola çá Suffit trial strengthen the interim estimates and conclusions¹⁸ that the rVSV-ZEBOV vaccine has high protective efficacy and effectiveness to prevent Ebola virus disease. The current report included data from 27 additional clusters; eight of which were randomly assigned to immediate or delayed vaccination. No vaccinees developed Ebola virus disease 10 days or more after randomisation, but cases occurred in unvaccinated comparators, both in randomised and non-randomised clusters. When we compared randomly assigned contacts and contacts of contacts vaccinated in immediate clusters (day 0) versus all eligible in delayed clusters, vaccine efficacy was 100%. These final analyses hence support the interim report efficacy results, indicating that ring vaccination with an effective vaccine can contribute as a control strategy for future outbreaks of Ebola virus disease.

Data from early phase 1–2 studies suggest that rVSV-ZEBOV is well tolerated in human beings and produces a rapid immune response after a single dose,^{32,33}

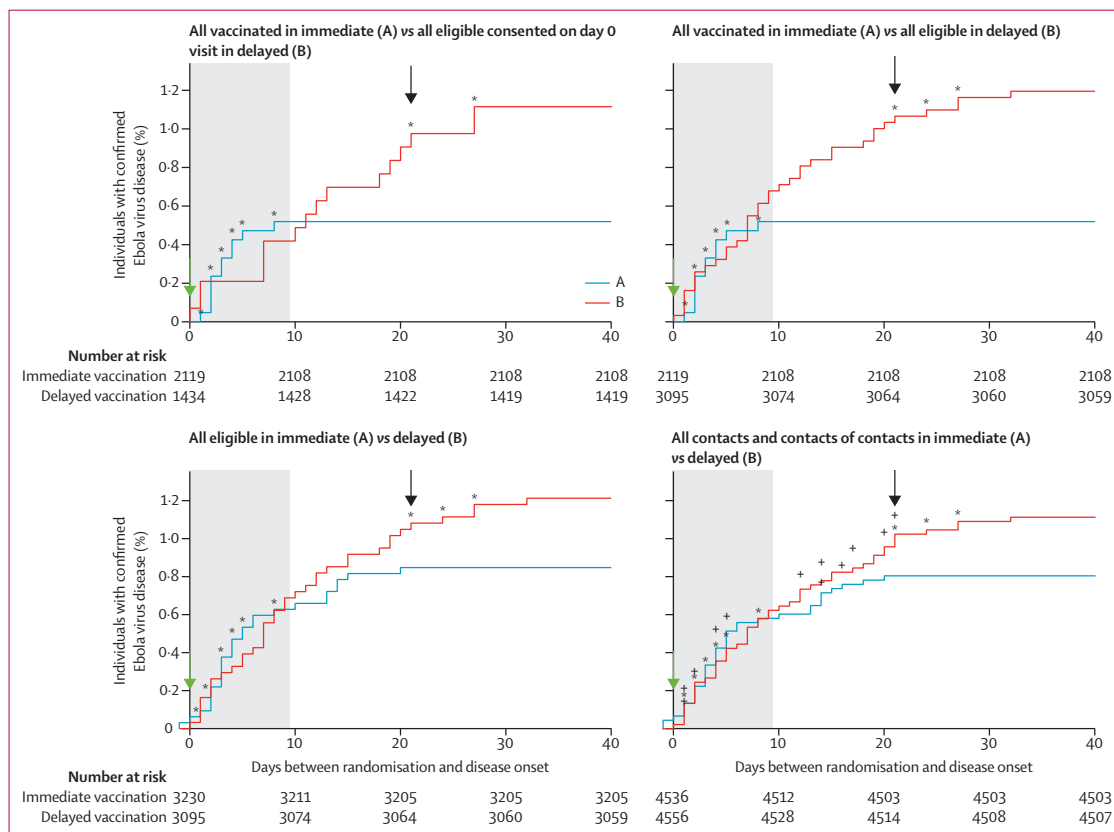


Figure 3: Kaplan-Meier plots for confirmed cases of Ebola virus disease in different study populations

Arrows show time of vaccination (at day 0 or day 21); the plus signs denote cases among non-eligible children and the stars denote cases among vaccinated individuals; the shaded area denotes the a priori defined lag time of 0–9 days.

with its short-term protection most likely mediated by innate immunity. One explanation for this finding is that innate immune activation by the vaccine might provide a window of protection that restricts virus replication in the essential period needed for the development of specific adaptive responses.¹¹

A devastating outbreak of Ebola virus disease is clearly not the ideal situation for doing a vaccine trial. The healthcare system in Guinea was strained, potential trial participants were worried about a candidate vaccine made by foreign people, and the Ebola virus disease response teams were facing security issues. Therefore, we made a deliberate decision to tailor the logistical implementation of the trial to local conditions.²⁰ The close collaboration with, and the support from, the Guinean National Authorities was a catalysing factor in the successful implementation of the trial. In addition, we made efforts to ensure full ownership and understanding by national authorities and communities through active community engagement and individual consent. Despite the challenges, our team was able to do the trial in compliance with good clinical practice and international standards.

We addressed common biases of cluster-randomised trials. Our analyses suggested no imbalances in the

demographic characteristics of the index cases or the risk factors for Ebola virus disease infection documented in the contacts and contacts of contacts, further supporting the hypothesis that any differences were due to a vaccine effect. A few differences remained between groups. Time to cluster definition was slightly shorter in the immediate vaccination group, which also had more high-risk contacts reported. All valid clusters enrolled were analysed, and more than 90% of vaccinees were followed up in all groups. To address recruitment bias, we finalised and closed the enumeration of eligible contacts and contacts of contacts in each cluster before cluster allocation. Although we implemented prospective recruitment, only contacts and contacts of contacts included in the cluster enumeration list were given the opportunity to provide informed consent. A different team obtained informed consent to minimise subversion. Participants were informed of the outcome of randomisation at the end of the informed consent process, and both immediate and delayed clusters were given identical information about the trial before consent.

The inclusion of temporarily absent contacts and contacts of contacts contributed to a moderate

	0–30 min	31 min to 3 days	4–14 days
Children aged between 6–<18 years (n=194)			
Arthralgia	0	3 (3.5%)	1 (9.1%)
Diarrhoea	0	0	1 (9.1%)
Fatigue	0	10 (11.6%)	1 (9.1%)
Fever	0	1 (1.2%)	1 (9.1%)
Headache	0	47 (54.7%)	4 (36.4%)
Induration	0	0	0
Injection pain	0	9 (10.5%)	0
Muscle pain	0	4 (4.7%)	1 (9.1%)
Myalgia	0	4 (4.7%)	1 (9.1%)
Vomiting	0	1 (1.2%)	0
Other adverse events	0	7 (8.1%)	1 (9.1%)
Total	0	86 (100.0%)	11 (100.0%)
Adults aged 18 years and older (n=5643)			
Arthralgia	3 (2%)	851 (13.5%)	79 (12.3%)
Diarrhoea	0	53 (0.8%)	15 (2.3%)
Fatigue	5 (3.3%)	1233 (19.5%)	112 (17.4%)
Fever	2 (1.3%)	8 (0.1%)	2 (0.3%)
Headache	41 (27.3%)	1563 (24.7%)	177 (27.5%)
Induration	0	1 (<1%)	0
Injection pain	70 (46.7%)	362 (5.7%)	8 (1.2%)
Muscle pain	7 (4.7%)	875 (13.8%)	55 (8.5%)
Myalgia	6 (4.0%)	816 (12.9%)	47 (7.3%)
Vomiting	0	21 (0.3%)	4 (0.6%)
Other adverse events	16 (10.7%)	537 (8.5%)	145 (22.5%)
Total	150 (100.0%)	6320 (100.0%)	644 (100.0%)

Data are n (%); individuals might have had more than one adverse event.

Table 5: Frequency of solicited adverse events by time since vaccination in children and adults

within-cluster percentage of vaccinees among the eligible contacts and contacts of contacts of 65.6% in immediately randomised clusters, 65.9% in delayed randomised clusters and 83.6% in non-randomised clusters. The higher uptake of vaccine among the contacts and contacts of contacts in non-randomised clusters might be attributable to public knowledge of the interim results as well as the inclusion of children aged 6 years and older.

Confirmation of cases with Ebola virus disease was done independently of the study team as part of the national surveillance of Ebola virus disease, throughout and beyond the follow-up period of the trial. Confirmatory retesting of samples of index cases and endpoints augmented the independence of the process.

Although eligible individuals in the delayed arm had two opportunities to consent (day 0 and day 21), those consenting at day 21 could only do so if they had not been diagnosed with Ebola virus disease in the intervening time. We therefore also presented a comparison of the vaccine effect with individuals in the delayed group who

gave consent during the first visit (day 0). Because only one additional case of Ebola virus disease was documented among those consenting late (on day 21), the estimated vaccine effect remained 100% but the lower 95% CI bound changed from 68.9% to 63.5%.

These results are the only efficacy data available for rVSV-ZEBOV, and for any Ebola virus disease vaccine, available from trials in human beings to date. Because of the challenges of implementing the trial, we decided not to attempt to collect biological samples from vaccinees for immunological analysis and therefore an individual-level correlation of protection analysis was unfortunately not possible. Such interpretation would also have been rendered difficult given that there were no break-through cases among vaccinees after day 10. The high levels of vaccine effect noted in this study are in line with findings from other studies, such as the phase 2 PREVAIL trial,³⁴ which used the same dose and route of administration and showed that 94% of 500 individuals who received the rVSV-ZEBOV vaccine seroconverted after a month. Results from animal studies with rVSV-ZEBOV vaccines have also shown consistently high and rapid protection.^{11,12} Our results will be further complemented by those from a cohort study to assess immune response after vaccination that we did in front-line workers in Guinea.

We designed this trial to have a high probability of generating meaningful data for the efficacy of the vaccine despite the low and declining incidence of Ebola virus disease. Our design attempted to address the challenge that the comparator group should not be denied access (at least indefinitely) to the experimental vaccine, an issue raised by ethics committees and others, and we opened eligibility for children as soon as preliminary safety data were available from phase 1 studies.²² In our final phase 3 analyses no serious safety signals were identified in children or adults.

A feature of the ring vaccination trial design is the potential to measure indirect protection within the clusters. Our data suggest that such indirect effect occurred, but the small sample size prevented a definitive conclusion. Nevertheless, the high efficacy of the rVSV-ZEBOV vaccine, as indicated by the randomised and non-randomised analysis, suggests that the Ebola ça Suffit trial itself had some contribution to foreshortening the epidemic of Ebola virus disease in west Africa by direct and indirect aversion of cases. The evidence from randomised and non-randomised clusters and the fact no cases of Ebola virus disease occurred 10 or more days after vaccination (through the 84 days follow-up period and from the indefinite surveillance system throughout the epidemic period) indicates substantial protection of rVSV-ZEBOV against Ebola virus disease. Ring vaccination was effective in contributing to controlling the Ebola virus disease outbreak. Results from mathematical modelling studies, which used the data from the ring vaccination trial, indicate that using ring vaccination within a surveillance and containment

strategy could be highly effective in controlling future outbreaks of Ebola virus disease.³⁵ The findings from Ebola ça Suffit showed that it is feasible to undertake efficacy trials in the challenging circumstances of epidemics. Vaccine trial designs using case-reactive strategies similar to those of the ring vaccination trial might have an application in future haemorrhagic fever outbreaks and in other infectious disease epidemics.

Contributors

IML, ME, AMH-R, WJE, CHW, M-PK, and J-AR conceived and designed the trial; SM, CHW, GN, XR, SH, AMH-R, IML, ME, WJE, AC, GE, ASV, ST, and J-AR contributed to the protocol and design of the study. J-AR, M-PK, MKK, AMH-R, BD, RG, and GN provided management and oversight of the trial as members of the study steering group. AMH-R coordinated the study design process and implementation of the trial on behalf of the study steering group. MD, MKK, and AS were coprincipal investigators. AMH-R, M-PK, SKé, MML, MD, MKK, AS, ASV, XR, GE, SH, ST, SKo, TM, CHW, SM, SVW, and GN contributed to the field implementation of the trial. MWC, SD, SG, and EK supported the laboratory testing and validation of endpoints. AC and IML did the statistical analyses. AC, IML, AMH-R, NED, CHW, WJE, ST, and PSG contributed to data interpretation. NED wrote the scripts for the statistical tests. AC, AMH-R, IML, CHW, WJE, J-AR, and M-PK contributed to the preparation of the report. ID and P-SG contributed to the implementation of the study. All authors critically reviewed and approved the final version.

Declaration of interests

WJE, AC, ME, and CHW have acted as unpaid advisors to WHO on Ebola vaccination, and report travel and accommodation paid for by WHO to attend meetings. WJE is a coinvestigator on the European Commission Innovative Medicines Initiative-funded EBOVAC trial of the Johnson & Johnson prime-boost Ebola vaccine candidate, for which he has received a grant from the European Commission Innovative Medicines Initiative, and his partner is an epidemiologist at GlaxoSmithKline, in a role unrelated to the company's development of an Ebola vaccine. AC and CHW have acted as unpaid advisors to the EBOVAC trial, for which CHW reports travel and accommodation paid for by the EBOVAC consortium to attend a meeting. AC and CHW have received non-financial support from Janssen outside the submitted work. SG received grants from the European Commission during the study. ST, SH, JE, and CHW received grants from Research Council of Norway during the study. MWC received Ebola virus research funding from the European Union and US Food and Drug Administration during the study. The other authors declare no competing interests.

Acknowledgments

We thank the people in Basse-Guinée for their participation, and the entire field, laboratory, and data management staff who worked tirelessly and in difficult conditions to successfully implement this trial. Merck Sharp & Dohme provided the vaccine used in the trial. We would like to acknowledge the support of the following organisations: Wellcome Trust, the UK Government through the Department of International Development, Guinean Ministry of Health, Norwegian Ministry of Foreign Affairs, US Department of Defence, Public Health Agency of Canada, Swiss Agency for Therapeutic Products, the Bill & Melinda Gates Foundation, Health Canada, the VSV Ebola Consortium (VEBCON), and the European Commission. We also thank Donald A Henderson*, Jeremy Farrar, Richard Peto, Tore Godal, Bruce Aylward, Djilali Abdelghafour, Oumou Bah Sow, Mohammed Belhocine, Pierre-Henri Bertoye, Yap Boum, Mar Cabeza-Cabrerizo, Rokiatu Dembele, Laura De Paoli, Aboubacar Sidiki Diakitè, Ahmadou Diallo, Mamoudou Harouna Djingarey, Julia Djonova, Pascal Frison, Melba Filimina Gomes, Myriam Grubo, Yper Hall, Raul David Hone, Raul Iraheta, Olivier Lapujade, Murray Lumpkin, Christine Maure, Corinne Merle, Nicholas Misso, Jérôme Mouton, Pierre Ndiaye, Bjørg Dystvold Nilsson, Marie-Pierre Preziosi, Vasee Moorthy, Jean-Marie Okwo-Bele, William Perea, Guenal Rodier, Maria Magdalena Guraib, Martina Rothenbühler, Abha Saxena,

Peter Smith, Kabiné Souare, Samba Sow, Graciela Spizzamiglio, Milagritos Tapia, Marie Tchaton, Guido Torelli, Bear Widler, Delayo Zomahoun, and many colleagues at WHO for their invaluable support with implementation of the trial; and all members of our scientific advisory group, our data and safety monitoring board, and the Guinea vaccine trial working group.

*Died on Aug 19, 2016.

References

- 1 WHO. Ebola virus disease fact sheet, 2016. <http://www.who.int/mediacentre/factsheets/fs103/en/> (accessed Nov 30, 2016).
- 2 Ministry of Health Guinea. Ebola situation, report 655, Jan 30, 2016. http://guinea-ebov.github.io/code/files/sitreps/GUINEA_EBOLA_SITREP%20N%20655%20DU%2030_Jan_2016.pdf (accessed Nov 30, 2016).
- 3 Kanopathipillai R, Henao Restrepo AM, Fast P, et al. Ebola vaccine—an urgent international priority. *N Engl J Med* 2014; **371**: 2249–51.
- 4 Marzi A, Feldmann H. Ebola virus vaccines: an overview of current approaches. *Expert Rev Vaccines* 2014; **13**: 521–31.
- 5 Jones SM, Stroher U, Fernando L, et al. Assessment of a vesicular stomatitis virus-based vaccine by use of the mouse model of Ebola virus hemorrhagic fever. *J Infect Dis* 2007; **196** (suppl 2): S404–12.
- 6 Wong G, Audet J, Fernando L, et al. Immunization with vesicular stomatitis virus vaccine expressing the Ebola glycoprotein provides sustained long-term protection in rodents. *Vaccine* 2014; **32**: 5722–29.
- 7 Jones SM, Feldmann H, Stroher U, et al. Live attenuated recombinant vaccine protects nonhuman primates against Ebola and Marburg viruses. *Nat Med* 2005; **11**: 786–90.
- 8 Feldmann H, Jones SM, Daddario-DiCaprio KM, et al. Effective post-exposure treatment of Ebola infection. *PLoS Pathog* 2007; **3**: e2.
- 9 Geisbert TW, Daddario-DiCaprio KM, Lewis MG, et al. Vesicular stomatitis virus-based Ebola vaccine is well-tolerated and protects immunocompromised nonhuman primates. *PLOS Pathog* 2008; **4**: e1000225.
- 10 Qiu X, Fernando L, Alimonti JB, et al. Mucosal immunization of cynomolgus macaques with the VSVdeltaG/ZEBOVGP vaccine stimulates strong ebola GP-specific immune responses. *PLOS One* 2009; **4**: e5547.
- 11 Marzi A, Robertson SJ, Haddock E, et al. VSV-EBOV rapidly protects macaques against infection with the 2014/15 Ebola virus outbreak strain. *Science* 2015; **349**: 739–42.
- 12 Marzi A, Hanley PW, Haddock E, Martellaro C, Kobinger G, Feldmann H. Efficacy of vesicular stomatitis virus–ebola virus post exposure treatment in Rhesus macaques infected with ebola virus makona. *J Infect Dis* 2016; **214** (suppl 3): S360–66.
- 13 Daddario-DiCaprio KM, Geisbert TW, Geisbert JB, et al. Cross-protection against Marburg virus strains by using a live, attenuated recombinant vaccine. *J Virol* 2006; **80**: 9659–66.
- 14 Geisbert TW, Geisbert JB, Leung A, et al. Single-injection vaccine protects nonhuman primates against infection with Marburg virus and three species of Ebola virus. *J Virol* 2009; **83**: 7296–304.
- 15 de Wit E, Marzi A, Bushmaker T, et al. Safety of recombinant VSV–Ebola virus vaccine vector in pigs. *Emerg Infect Dis* 2015; **21**: 702–04.
- 16 Geisbert T, Daddario-DiCaprio K, Geisbert J, et al. Vesicular stomatitis virus-based vaccines protect nonhuman primates against aerosol challenge with Ebola and Marburg viruses. *Vaccine* 2008; **26**: 6894–900.
- 17 Fenner F, Henderson DA, Arita I, Jezek Z, Ladnanyi ID, World Health Organization. Smallpox and its eradication. 1988. <http://apps.who.int/iris/handle/10665/39485> (accessed Nov 30, 2016).
- 18 Henao-Restrepo AM, Longini IM, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. *Lancet* 2015; **386**: 857–66.
- 19 Osterholm MT, Moore KA, Kelley NS, et al. Transmission of Ebola viruses: what we know and what we do not know. *mBio* 2015; **6**: e00137–15.
- 20 Ebola ça Suffit ring vaccination trial consortium. The ring vaccination trial: a novel cluster randomised controlled trial design to evaluate vaccine efficacy and effectiveness during outbreaks, with special reference to Ebola. *BMJ* 2015; **351**: h3740.

- 21 WHO. Contact tracing during an outbreak of Ebola virus disease. September, 2014. <http://www.who.int/csr/resources/publications/ebola/contact-tracing/en/> (accessed Dec 22, 2014).
- 22 VEBCOM phase 1 study, Lambarene, Gabon (PACTR2014000089322), unpublished data.
- 23 WHO. Case definition recommendations for Ebola or Marburg virus disease. 2014. <http://www.who.int/csr/resources/publications/ebola/ebola-case-definition-contact-en.pdf> (accessed July 22, 2015).
- 24 WHO. Laboratory diagnosis of Ebola virus disease, interim guideline, 19 September 2014. http://apps.who.int/iris/bitstream/10665/134009/1/WHO_EVD_GUIDANCE_LAB_14.1_eng.pdf (accessed Aug 20, 2016).
- 25 WHO. Ebola vaccine chosen for planned Guinea clinical trial, 2016. http://www.who.int/medicines/ebola-treatment/guinea_ebola_trial/en/ (accessed Aug 18, 2016).
- 26 WHO Ebola Response Team. Ebola virus disease among children in West Africa. *N Engl J Med* 2015; **372**: 1274–77.
- 27 WHO Ebola Response Team. Ebola virus disease among male and female persons in West Africa. *N Engl J Med* 2016; **374**: 96–98.
- 28 Krause PR. Interim results from a phase 3 Ebola vaccine study in Guinea. *Lancet* 2015; **386**: 831–33.
- 29 Zhang Y, Feng S, Cowling BJ. Changes in the primary outcome in Ebola vaccine trial. *Lancet* 2016; **387**: 1509.
- 30 Kieny MP, Longini IM, Henao-Restrepo AM, Watson CH, Egger M, Edmunds WJ. Changes in the primary outcome in Ebola vaccine trial: authors reply. *Lancet* 2016; **387**: 1509–10.
- 31 The R Project for Statistical Computing, r version 3.3.1. <https://www.r-project.org/s/> (accessed July 1, 2016).
- 32 Regules JA, Beigel JH, Paolino KM, et al. A recombinant vesicular stomatitis virus Ebola vaccine—preliminary report. *N Engl J Med* 2015; published April 1. DOI:10.1056/NEJMoa1414216.
- 33 Agnandji ST, Huttner A, Zinser ME, et al. Phase 1 trials of rVSV Ebola vaccine in Africa and Europe. *N Engl J Med* 2016; **374**: 1647–60.
- 34 National Institutes of Health, National Institute of Allergy and Infection Diseases. Experimental ebola vaccines well tolerated, immunogenic in phase 2 study. 2016; news release, Feb 23. <https://www.niaid.nih.gov/news/newsreleases/2016/Pages/CROI-PREVA11.aspx> (accessed Aug 31, 2016).
- 35 Ajelli M, Merler S, Fumanelli L, et al. Spatio-temporal dynamics of the Ebola epidemic in Guinea and implications for vaccination and disease elimination: a computational modeling analysis. *BMC Med* 2016; **14**: 130.

Immunization Competencies Initiative

Competencies of the Immunization Technical Workforce

DRAFT FOR SAGE MEETING APRIL 2017

Covering only National level

Supporting the objective of the Expanded Program on Immunization

Dedicated to the health care workers around the world whose perseverance and care protect children from vaccine preventable diseases

EPI Services	3
Summary of the work that is done in a successful expanded program on immunization	3
Glossary of Terms	3
About this Document.....	5
Assumptions	5
The Work and Competencies by Level	6
National Level.....	6
<u>Service Delivery</u>	6
<u>Policy, Planning, & Finance</u>	6
<u>Communications/Advocacy</u>	7
<u>Human Resources and Performance Management</u>	8
<u>Vaccine Supplies and Logistics</u>	9
<u>Immunization and Injection Safety</u>	9
<u>Disease Surveillance, Investigation and Response</u>	10
<u>Monitoring, Evaluation and Data Use</u>	11
<u>Cross Cutting: Management & Leadership</u>	12
<u>Cross Cutting: Vaccine Preventable Diseases</u>	12
Acknowledgements	13
References	13
Working Group	15

EPI Services

Summary of the work that is done in a successful expanded program on immunization

1. Immunization Service Delivery: Routine and Supplemental activities
2. Policy, Planning and Finance
3. Human Resources and Performance management
4. Communications and Advocacy
5. Vaccines, Supplies and Logistics
6. Immunization and Injection Safety
7. Disease Surveillance, Investigation and Response
8. Monitoring, Evaluation and Strategic Information

A successful EPI requires a workforce competent in these areas as well as cross cutting competencies in:

1. Management and Leadership
2. Vaccine Preventable Diseases

Glossary of Terms

Competency

Knowledge, skills and attitude required for successful work performance

Work

The tasks that are required for an organization to meet its objectives

Summary of key features of a successful EPI by domains and organizational level

	Health Facility	District/Local	Province/State	National
Service Delivery	Implemented services and immunized community	Implementation of policies and SOPS to ensure service delivery	Implementation of policies and SOPS to ensure service delivery	Implementation of policies and SOPS to ensure service delivery
Policy, Planning and Finance	Quality micro plans	Microplanning, resource management, services integration and implementation	Evidence based policies, planning, and micro plans Resource management	Annual and cMYP planning, priority and policy setting Financial management
Communications and Advocacy	Mobilized community	Demand creation and community engagement	Advocacy, collaboration, communication strategies	National and partner advocacy and communication
Human Resources and Performance Management	Skilled motivated worker	Staffing, training and supervision	Staffing, training and supervision	National HR, training and performance support systems
Vaccines, supplies & logistics	Available supplies in good condition	Cold chain, supplies and equipment planning and monitoring	Inventory forecasting, planning and management Storage and distribution	Vaccines and supplies procurement policies. Forecasting, planning and management
Immunization and Injection Safety	Safe immunization practices	Supervision of safety measures, AEFI reporting and response	Safety measures implementation and monitoring. AEFI surveillance, reporting and response	National policies for quality handling to ensure safe and effective vaccines. AEFI surveillance, reporting and response
Disease Surveillance and Response	Accurate records, reports, response	Disease surveillance, investigation and response	Disease surveillance, investigation and response	Disease surveillance, investigation and response. Laboratory collaboration
Monitoring, Evaluation and Data Use	Accurate records and reports Use and continuous quality improvement	Quality data collection and use, monitoring and feedback	Quality data for decision making, monitoring and feedback	Data management, Established M&E indicators, national standards and tools, Evidence based decision making, program evaluation

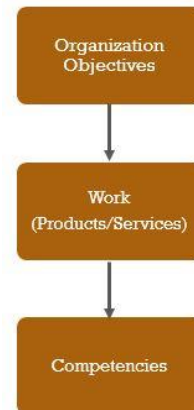
About this Document

This document is intended to support the assessment, design, development and evaluation of workforce development initiatives. It is based on a framework that links the competencies of the workforce to the objectives of an organization.

An organization has a primary objective.

To achieve that objective, work is done.

The organization requires a workforce with the competencies to complete the work.



Thus, this document describes the **work** as well as the **competencies** that are required at four major levels of a country's Expanded Program on Immunization system.

Assumptions

- The EPI functions within the broader health system of a country
- Underlying governance, stability and national infrastructure are essential to vaccination systems
- Interaction, interaction, communication, feedback are critical between levels and specialty areas
- Decentralization may move some attributes between national, provincial and district levels
- The work done at each level is not necessarily done by a single individual
- Additional competencies that are not specific to immunization, such as information technology, laboratory systems, accounting, and human resources management, are essential to a successful EPI.

Notes:

- Supervision for all domains is included in human resources domain
- Recording and program monitoring is included in the Monitoring/Evaluation/Data Use domain
- Data or information use including prioritization is included in the Monitoring/Evaluation/Data Use section and is related to all domains including surveillance

The Work and Competencies by Level

National Level

Service Delivery

The Work

It is assumed that national level staff do not work with service delivery directly. Rather the work described below supports quality service delivery at the lower levels

Policy, Planning, & Finance

The Work

Set national vision
 Set priorities, targets and strategies
 Ensure appropriate integration of EPI plans into broader HSS plans
 Define and revise national policies and guidelines based on evidence, ex. routine immunization schedule, equitable access
 Adapt and ensure national policies comply with international regulations/guidelines
 Plan programs and projects with key stakeholders, ex:

- Macroplan (annual and multiple year)
- SIAs
- Vaccine introduction

Analyze, interpret and manage finances; Cost program needs
 Write proposals, ex GAVI applications, public/private partnerships
 Budget and monitor resources, expenditures and fund flow
 Coordinate with and provide support for national advisory groups, ex, National Immunization Technical Advisory Group (NITAG), Interagency Coordinating Committee (ICC)
 Coordinate with Ministry of Health (MOH), Ministry of Finance (MOF), regulatory, legislative and other authorities
 Advise on vaccine research & development and introduction of new vaccine
 Coordinate with other programs to integrate services and/or strategies
 Coordinate with national Incident Management Structure or Emergency Operations

Competencies

Set strategic targets and priorities
 Make programmatic decisions based on evidence
 Write a policy paper or regulation
 Develop short and long term strategic and operational plans
 Conduct financial planning, analysis, and interpretation of financial data
 Develop a national budget
 Plan and manage a national project, such as introduction of new vaccine, coverage survey or national immunization days
 Oversee a national immunization schedule
 Implement plans, programs and policies

Communications/Advocacy

The Work

Advocate to MOH, MOF, government sectors (ex. zoning, transportation routes, national education policies)
 Participate in Immunization Coordinating Committee, national & global alliances
 Conduct resource mobilization
 Develop national risk, demand creation, and other communication strategies
 Monitor population knowledge, attitudes and practices
 Conduct communication research at national and local level
 Share best practices in immunization delivery with lower levels
 Interact with media to communicate immunization messages of national importance, such as special initiatives, success stories, and needs for improvement
 Develop, implement and evaluate demand creation initiatives based on evidence

Competencies

Communicate in a credible, effective way to stakeholders and staff
 Build trust-based relationships with internal and external partners
 Complete a grant application
 Design and implement a national communication campaign
 Interact with media
 Negotiate with stakeholders to foster coordinated decision making and multi-partner activities
 Deliver a formal or extemporaneous technical presentation to a decision maker, senior official, or external partner

Human Resources and Performance Management

The Work
Set national policy for HR per MOH guidelines Staff national positions in coordination with national human resource authorities Define career development plans in coordination with national human resource authorities Provide guidelines and indicators for performance management Conduct regular staff performance reviews and provide constructive feedback Plan and provide supportive supervision for provincial level employees Develop and maintain job descriptions Coordinate training and on-the-job support and guidelines Support innovation and learning

Competencies
Supervise staff performance & development Write a job description Conduct a job interview Determine human resource needs at all levels and take actions to fill gaps Manage a performance review system at the national level Conduct succession planning Establish HR performance indicators Design a VPD staff training program

Vaccine Supplies and Logistics**The Work**

Forecast vaccine, cold chain, other supply & logistical needs
 Develop & communicate procurement, transport, storage and wastage guidelines
 Procure vaccines, supplies, and equipment, (includes ordering receipt, customs)
 Store vaccine in safe places and in effective temperature control
 Work with partners to advocate for vaccine security/ affordable vaccines
 Monitor cold chain using vaccine vial monitors and temperature monitoring devices
 Ensure and maintain logistics management information systems

Competencies

Coordinate with others on procurement
 Forecast vaccine, cold chain, supply & logistical needs
 Develop and implement a vaccine management plan

- storage/warehousing
- vaccine distribution
- equipment maintenance
- equipment monitoring
- supply chain inventory monitoring
- temperature monitoring
- regulation compliance

 Procure vaccine & supplies
 Develop storage, transportation and wastage processes
 Maintain logistics management information systems
 Conduct vaccine management assessments

Immunization and Injection Safety**The Work**

Develop, communicate and monitor safety policies and guidelines, including AEFI
 Develop waste management plans and guidelines
 Coordinate with the National Regulatory Authority (NRA)
 Build private, public and international partnerships on safety
 Develop SOPs and reporting templates using global standards
 Ensure quality, effectiveness and safety of vaccines
 Develop and manage AEFI surveillance, reporting and response system

Competencies

Develop and monitor safety policies
 Develop communicate, implement and monitor vaccine safety policies
 Conduct a vaccine safety assessment
 Manage AEFI surveillance, reporting and response system
 Assess causality
 Develop waste disposal strategies & policies
 Develop a crisis communication plan in order to respond to vaccine adverse events

Disease Surveillance, Investigation and Response

The Work

Develop, communicate and monitor VPD disease surveillance, investigation and response guidelines
 Develop VPD surveillance system processes and tools
 Conduct surveillance summary & trend analysis
 Complete international reporting
 Monitor quality of the surveillance system
 Integrate with laboratory
 Coordinate with integrated and other disease surveillance systems
 Conduct epidemiological studies
 Integrate with national health management information

Competencies

Design set up and monitor a VPD surveillance/data system
 Develop, set up and monitor investigation and response systems
 Interpret quantitative data to inform decision making
 Conduct surveillance summary & trend analysis
 Conduct a surveillance system quality assessment
 Conduct epidemiological studies

Monitoring, Evaluation and Data Use**The Work**

Design and manage immunization components within national health management information system.

Manage and interpret data

Collaborate with national vital statistics

Develop and implement quality assurance tools (ex, checklists)

Periodically evaluate program using international EPI reviews, data assessments and related operational assessments

Plan and implement vaccination coverage surveys

Develop monitoring and evaluation plans and tools

Evaluate program components, strategies and interventions

Monitor policy implementation, performance indicators and disease occurrence.

Report on indicators to the national MOH, international; and/or regional bodies; ex Joint Reporting Form

Conduct studies and research to inform national policy,

- Burden of disease/vaccine introduction
- Operational
- Clinical trials
- Economic
- Other special studies

Provide feedback on reported data, quality, performance indicators and interpretation

Conduct regular programmatic reviews; ex, meetings with provincial staff; other site visits

Make programmatic decisions based on quality evidence & report

Competencies

Set standards for immunization data and information systems

Manage data

Develop monitoring & evaluation plans

Use quantitative and qualitative methods to monitor EPI program quality

Develop checklists and monitoring tools (ex templates, dashboards)

Design and conduct a program evaluation

Design and lead a quality improvement project

Collaborate with national vital statistics

Conduct data quality assessments (ex, DQA, DQS)

Set data archiving and sharing policies

Use data analysis to set priorities and take action

Prepare performance reports

Conduct an EPI performance review

Disseminate findings to stakeholders

*Cross Cutting: Management & Leadership***Competencies**

Define and communicate the organization's vision, mission and strategies
 Recognize trends and opportunities in immunization practice and in leadership and apply them to the national EPI
 Motivate others to follow a shared goal
 Integrate core values, integrity, equity and accountability throughout all organizational practices
 Prioritize and delegate work to others
 Create an open and trust-based work environment
 Develop networks and builds alliances
 Think strategically: formulate objectives and priorities, and implement plans consistent with the long-term interest of the organization
 Lead a work team
 Solve problems and deal effectively with uncertainty

*Cross Cutting: Vaccine Preventable Diseases***Competencies**

Apply knowledge of key epidemiologic and clinical features of each vaccine-preventable disease to making decisions
 Access and use information regarding future vaccines, immunization trends and policies
 Apply PH sciences (epidemiology, biostatistics, social sciences, informatics) to policy decisions and planning
 Integrate knowledge about the main steps in vaccine development and evaluation into decision making
 Describe diseases and vaccines to an audience with minimal or no science knowledge (political leaders, media), other medical professionals, and professional organizations
 Be familiar with and access current WHO position papers, recommendations and other resources
 Provide evidence on the need for a new or controversial vaccine

Acknowledgements

References

- Bailey, E. (2007). *Improving Organizational Performance*. LavaCon.
- Barbara Arrington, J. K., Mikki Brewster, Judy Bentley, Mary Kane, Catherine Van Brunschot, Melissa Burns, Kathleen Quinlan, and Ross C. Brownson (2008,). "Building a Local Agenda for Dissemination of Research Into Practice." *Journal of Public Health Management Practice* 14(2): 185-192.
- Bartram, D. (2005). "The Great Eight Competencies: A Criterion-Centric Approach to Validation." *Journal of Applied Psychology* 90(6): 1185-1203.
- Centers for Disease Control and Prevention, Office for State, Tribal, Local and Territorial Support (2014). *The 10 Essential Public Health Services: An Overview*.
- Chiauzzi, E., et al. (2011). "Identifying primary care skills and competencies in opioid risk management." *J Contin Educ Health Prof* 31(4): 231-240.
- Daniel J. Kealey, D. R. P., Doug MacDonald, and Thomas Vulpe (2003). "Instituting a Competency-Based Training Design and Evaluation System." *Performance Improvement* 42(5).
- Fleishman, E. A. (1975). "Toward a Taxonomy of Human Performance." *American Psychologist*: 1127.
- Gayeski, D. M., et al. (2007). "Bringing competency analysis into the 21st century." *Performance Improvement* 46(7): 9-16.
- Joke Haafkens, Y. B., Malin Eriksson, Heiko Becher, Heribert Ramroth and John Kinsman (2014). "Training needs for research in health inequities among health and demographic researchers from eight African and Asian countries." *BMC Public Health* 14: 1254.
- Kendall, P. C. S. a. L. M. (1963). "Retranslation of Expectations: An Approach to the Construction of Unambiguous Anchors for Rating Scales." *Journal of Applied Psychology* 47(2): 149-155.
- Lievens, F., et al. (2004). "Easing the Inferential Leap in Competency Modelling: The Effects of Task-related Information and Subject Matter Expertise*." *Personnel Psychology* 57(4): 881-904.
- Management Sciences for Health. *Leading & Managing Framework*, USAID.
- Maxine Whittaker, R. E. M., and Anna Rodney (2013). *Mapping health information system competencies for health workers in low- and middle-income countries*. Working Paper Series. H. I. S. K. Hub, School of Population Health University of Queensland
- McClelland, D. C. (1998). "Identifying Competencies with Behavioral-Event Interviews." *American Psychological Society* 9(5).

Michael A. Campion, A. A. F., Brian J. Ruggeberg, Linda Carr, Geneva M. Phillips, and Ronald B. Odman (2011). "Doing Competencies Well: Best Practices in Competency Modeling." *Personnel Psychology* 64: 225-262.

Place, J. (2014). *Competency Assessment for Tier 1 Public Health Professionals*, Public Health Foundation.

Public Health Agency of Canada (2008) *Immunization Competencies for Health Professionals*. ISBN 978-1-100-10282-5

Salisbury, D. M., et al. (2002). "Vaccine programmes and policies." *Br Med Bull* 62: 201-211.

Slonim A, W. F., Quinlan KM, Smith SM (2010). "Designing Competencies for Chronic Disease Practice." *Preventing Chronic Disease Public Health Research, Practice and Policy* 7(2).

The Council on Linkages between Academia and Public Health Practice. (2014). *Core Competencies for Public Health Professionals*.

Trochim, W. M., et al. (2006). "Practical challenges of systems thinking and modeling in public health." *Am J Public Health* 96(3): 538-546.

United Kingdom Department of Health, Social Services and Public Safety, Royal College of Nursing. (2005) *National Minimum Standards for Immunisation Training*. ISBN 0-901144-73-8

Whiteside, D. L. a. K. (2004). "Bringing Sense to Competency Definition and Attainment." 43(7).

Winiecki, D. J. (2015). "Comparing a Few Behavior Engineering Models." *Performance Improvement* 54(8): 6-14.

World Health Assembly (2012). *Global Vaccine Action Plan Annex 6: The Monitoring and Evaluation/Accountability Framework*: 124.

World Health Organization, (2016). *Global Routine Immunization Strategies and Practice (GRISP)*

World Health Organization, (2014). "The immunization programme that saved millions of lives." *Bulletin* 92:314–315. doi: <http://dx.doi.org/10.2471/BLT.14.020514>

World Health Organization, (2008). *Training for Mid-level Managers (MLM)*.

World Health Organization, (2014). *Principles and considerations for adding a vaccine to a national immunization programme*.

Working Group

Name	Affiliation
Molly Abbruzzese	Bill and Melinda Gates Foundation
Johannes Ahrendts	GAVI, the Vaccine Alliance
Jhilmil Bahl	World Health Organization
Amalia Benke	Centers for Disease Control and Prevention Global Immunization Division
Lora Davis	Centers for Disease Control and Prevention Global Immunization Division
Dan Ehlman	Centers for Disease Control and Prevention Global Immunization Division
Lee Hampton	Centers for Disease Control and Prevention Global Immunization Division
Jennifer Hamborsky	Centers for Disease Control and Prevention National Center for Immunization and Respiratory Diseases, Immunization Services Division
Margaret Hercules	Centers for Disease Control and Prevention Global Immunization Division
Robert Kindoli	PATH
Arzu Koseli	International Children's Center
Dharmesh Lal	Public Health Foundation of India
Carla Lee	Centers for Disease Control and Prevention Global Immunization Division
William Mbabazi	African Field Epidemiology Network
Chris Morgan	Burnet Institute
Anthony Onimisi	World Health Organization
Susana Panero	Centers for Disease Control and Prevention Global Immunization Division
Sangay Phuntsho	Kingdom of Bhutan MOH
Alice Pope	Centers for Disease Control and Prevention Global Immunization Division
Alba Maria Ropero	Pan American Health Organization
Tove Ryman	Bill and Melinda Gates Foundation
Hardeep Sandhu	Centers for Disease Control and Prevention Global Immunization Division
Lorraine Shamalla	UNICEF
Lora Shimp	John Snow, Inc.
Steve Stewart	Centers for Disease Control and Prevention Global Immunization Division
Stephanie Tavitian	Centers for Disease Control and Prevention Global Immunization Division
Denise Traicoff	Centers for Disease Control and Prevention Global Immunization Division

Special thanks to the health care staff in Ghana, Jordan, and Kenya whose insight, gained during interviews, shed light on the work and the competencies that are required to deliver quality immunization services. We are also grateful to the regional and national staff of WHO SEARO and WPRO for sharing their wisdom.

SAGE APRIL 2017

NATIONAL IMMUNIZATION TECHNICAL ADVISORY GROUPS

Background Paper

Contents

1. Acronyms	2
2. Introduction	3
3. Background.....	3
NITAG definition	3
Minimum criteria of functionality	4
Effectiveness of NITAGs	4
4. Update on the current situation regarding establishment of NITAGs	5
Data source	5
Results.....	6
Interpretation	9
5. Issues and challenges faced by countries establishing or strengthening a NITAG	10
6. Partners roles and investments in supporting countries to establish and strengthen NITAGs	16
Partner strategies	17
Future plans	30
7. Summary and Way forward	31
8. Annexes.....	35
NITAG achievements: Country examples	35
Republic of Moldova NITAG.....	35
Timor Leste NITAG	35
Cote D'Ivoire NITAG	36
Mozambique NITAG.....	38
9. References	41

1. Acronyms

AMP-HPID	Agence de Médecine Préventive-Health Policy and Institutional Development Unit, WHO collaborating center for evidence informed immunization policy-making
AFRO	WHO African Regional Office
AMRO	WHO American Regional Office
CDC	US Centers for Disease Control and Prevention
ECDC	European Center for Disease Prevention and Control
EMRO	WHO Eastern Mediterranean Regional Office
EPI	Expanded Programme on Immunization
EURO	the WHO European Regional Office
GNN	Global NITAG Network
HSIS	Health Systems and Immunization Strengthening
HSS	Health Systems Strengthening
HTA	Health Technology Assessment
ICC	Inter-agency Coordinating Committees
IVI	International Vaccine Institute
JA	Joint Appraisal
MIC	Middle Income Country
NITAG	National Immunization Technical Advisory Group
PAHO	Pan American Health Organization
PIVI	Partnership for Influenza Vaccine Introduction
ProVac	Promoting [of] evidence-based decisions about Vaccine introductions Initiative
RAVIN	Rotavirus Accelerated Vaccine Introduction Network
RITAG	Regional Immunization Technical Advisory Group
SAGE	Strategic Advisory Group of Experts (on immunization)
SEARO	WHO South-East Asian Regional Office
SIVAC	Supporting Independent Immunization and Vaccine Advisory Committees Initiative
TCA	Tailored Country Assistance
USAID	the United States Agency for International Development
WPRO	WHO Western Pacific Regional Office

2. Introduction

For more than 10 years, WHO has been recommending its Member States to establish National Immunization Technical Advisory Groups (NITAG) or equivalent independent groups as a way to improve quality and ownership of national immunization programmes.

This recommendation initially endorsed by the Strategic Advisory Group of Experts (SAGE) on Immunization at the global level was then translated at regional levels through Regional Committee resolutions and Regional Technical Advisory Group recommendations. The Global Vaccine Action Plan (GVAP) objective of “all countries having a functional NITAG by 2020” was then endorsed by all Member States in 2012 at the 65th World Health Assembly. Regional committees followed by endorsing regional vaccine action plans most of which also contained specific targets for establishing NITAGs¹. Experience during the last decade has shown that establishing and strengthening NITAGs is critical for improving leadership in making informed decisions about the introduction and financial sustainability of vaccines.

In October 2016, as part of its mid-term review of the GVAP implementation, SAGE took note of the good progress made towards the achievement of this objective as of end 2015 with steady progress in the period 2010-2015 but that the GVAP 2020 objective for NITAGs will not be achieved without additional efforts from countries and partners. The mid-term report was SAGE’s first recommendation to Member States asking them to demonstrate stronger leadership and governance of national immunization systems and urging countries to establish NITAGs.

The NITAG session will update SAGE on progress achieved in the establishment and strengthening of NITAGs, the successes and challenges countries are facing, and the efforts and plans from the partners to achieve the GVAP 2020 goals. SAGE is being requested to provide guidance to countries and partners to ensure that the GVAP ambitious, yet realistic, goal of having all countries with a functional NITAG is achieved by 2020.

This document builds on partners input and attempts to provide an overview of the status of NITAG strengthening and to present challenges faced by countries and opportunities. It also presents the support provided by partners, the challenges they face and future plans and presents the way forward.

3. Background

NITAG definition

Decisions on what vaccines are included in national vaccination schedules, how to optimize the public health impact of those vaccines, and adjust existing schedules should be unbiased, comprehensive and systematic, and based on evidence-based criteria. Formally constituted national technical advisory bodies, often referred to as NITAGs, are multidisciplinary groups of national experts responsible for providing independent, evidence-informed advice to health authorities on all

¹ Regional targets are 90% of countries with a functioning NITAG by 2020 [European Region], all countries by 2017 [African Region], all countries by 2020 [Americas Region]; other regions (e.g., South-east Asia Region) which already have NITAGs in all Member States, set targets toward strengthening of existing NITAGs.

policy-related issues for all vaccines across all populations. Although each country will adjust its NITAGs roles and responsibilities based on its own needs and resources, the main role of NITAGs is to collect, review, assess and organize scientific evidence on specific vaccine-related topics in the form of recommendations to national health authorities, that take into account the local epidemiologic and social contexts. Other possible roles of NITAGs are to advise on implementation of national immunization programmes and to monitor programme impact.

Minimum criteria of functionality

As a proxy, a functional NITAG has been defined as one that meets all of the six following process indicators agreed upon in 2010 by WHO and its partners involved with the strengthening of NITAGs:

1. legislative or administrative basis for the advisory group;
2. formal written terms of reference;
3. at least five different areas of expertise represented among core members;
4. at least one meeting per year;
5. circulation of the agenda and background documents at least one week prior to meetings;
6. mandatory disclosure of any conflict of interest

These six indicators do not guarantee the functionality of the NITAG but have been agreed upon as a minimum set of indicators that will allow for monitoring of progress at the global level. As NITAGs mature at the global level, these basic process indicators will need to be adjusted over time.

Effectiveness of NITAGs

Although meeting basic criteria of functionality is necessary, NITAG performance is a combination and balance of the following elements of NITAG capacity: 1) to hold meetings regularly and issue recommendations in a timely manner; 2) to use the best available evidence and produce relevant recommendations in a given national context; and 3) to influence immunization policy decisions. For this reason, a more comprehensive set of indicators for assessing NITAG functionality, performance, outcomes and outputs was developed in 2013 by WHO, the Agence de Médecine Préventive Health Policy and Institutional Development Centre (AMP-HPID) which is a WHO Collaborating Centre, and other partners. Since this time, updated versions of this more comprehensive set of indicators (in the form of an evaluation tool) has been developed and used for country self-assessment and by partners to provide more insight into the functioning and effectiveness of NITAGs. The most recent version of the NITAG Assessment Tool is available on the NITAG Resource Center² (<http://www.nitag-resource.org/>), a global platform containing NITAG related information and supported by AMP-HPID.

At the 11–12 May 2016 international NITAG meeting, there was a strong call by countries to proceed with the establishment of a global NITAG network (GNN), which may accelerate progress on strengthening NITAGs and in evaluation of their NITAGs using the evaluation tool developed by the WHO Collaborating Centre AMP-HPID.

²NITAG resource center, Evaluation Tool: http://www.nitag-resource.org/media-center/document/1517-evaluation-tool-for-national-immunization-technical-advisory-groups-nitags?page=1&disease=0&document_type=0&topic=0&country=0&keyword=0&author=0&source=0&document_language=0&search=evaluation+tool

4. Update on the current situation regarding establishment of NITAGs

Data source

The process indicators outlined above, related to the establishment of NITAGs, have been included annually in the WHO-UNICEF Joint Reporting Form since 2011 (data for 2010). In this summary of information from Member States regarding the existence of a NITAG, the specific criteria are derived from the 2016 JRF with data collection for 2015 and compared with JRF data collected for previous years. For those Member States that did not submit or fully complete the JRF, information from the previous year's JRF was used. In the 2017 JRF (data for 2016), two additional questions were added to the data collection, specifically on whether the country conducted a NITAG assessment and what tool was used to conduct the assessment; these data will be available for future analyses.

The denominator used to calculate the proportion of NITAGs in existence is the number of Member States that completed the NITAG-related section of the JRF. The results are presented by WHO region, World Bank national income status categories and population size. Population figures are those from the United Nations Population Division³.

As highlighted in the previous GVAP Secretariat Annual Report 2016⁴ these results are subject to data limitations including some lack of data completion, the absence of a systematic data validation process with national counterparts and some confusion with the country Inter-agency Coordinating Committee (ICC). This confusion was actually documented, and has diminished over time. An increasing number of countries have corrected the information provided during previous years and corrections were retrospectively applied to the reported data for the previous years concerned. In order to assess the evolution of NITAG implementation and functionality since 2010, a thorough data cleaning was conducted based on consistency of responses on the overall time trend with final approval at country level.

When Member States report the existence of a NITAG with formal terms of reference or the existence of a NITAG with a formal administrative or legislative basis, data should be less susceptible to reporting bias than the mere reporting of the existence of a NITAG, and therefore the number of such groups should be closest to the actual number with respect to the existence of a NITAG. The number of Member States reporting the existence of a NITAG which complies with all six indicators is also less susceptible to reporting bias/error.

The description of the current NITAG situation is based on the GVAP Annual Secretariat Report 2016⁴ and updated from the member states reported data (through the WHO UNICEF JRF) as of 18 November 2016.

³ World population prospects: The 2012 revision [CD-ROM]. New York: United Nations, Department of Economic and Social Affairs, Population Division; 2013.

⁴ Global Vaccine Action Plan Secretariat Annual Report 2016

http://www.who.int/immunization/global_vaccine_action_plan/gvap_secretariat_report_2016.pdf?ua=1

Results

HIGHLIGHTS (as of 18 November 2016)

- A total of 79 Member States (including 50 developing countries and five low-income countries) reported access to a National Immunization Technical Advisory Group (NITAG) that met all six process indicators by end 2015, representing a 88% increase over the 42 countries reported on in 2010.
- A total of 116 (60%) Member States (accounting for 88% of the global population) reported the existence of a NITAG with an administrative or legislative basis;
- There has been minimal change in the number of countries meeting the six process indicators since 2014 (9 new countries met the six functionality criteria, while 10 countries dropped from the list – mostly due to not holding a meeting in 2015).
- Although there has been some progress in allowing small Member States to benefit from subregional or other Member States' advisory groups (e.g., subregional NITAGs are now active in small Caribbean countries), a formalized approach is still lacking.

As of 18 November 2016, 190 (98%) Member States had completed the 2016 JRF⁵ reporting immunization-related data for 2015, and 187 (96%)⁶ provided a response to at least one of the NITAG-related questions. Among the Member States that did not submit their JRF or their NITAG-related data for 2015, all of them had reported NITAG data in the past two years (i.e. data for 2013 and 2014). Therefore, data for 2013⁷ and 2014 were included in the 2015 data set for these Member States. Monaco reported using the French NITAG and therefore data from France were included in the data set for Monaco. It is not clear from the JRF if other small states in other regions rely on a neighbouring country's NITAG like Monaco and France. As a result, data for 194 Member States were available for the analysis as presented in Figure 1 and Table 1. Table 1 also presents the 2015 NITAG-related indicators status at the global and regional levels. The comparison between 2010 and 2015 is only provided at global level as progress encountered in some regions prior to 2010 could lead to spurious interpretation of the trends when broken down by region.

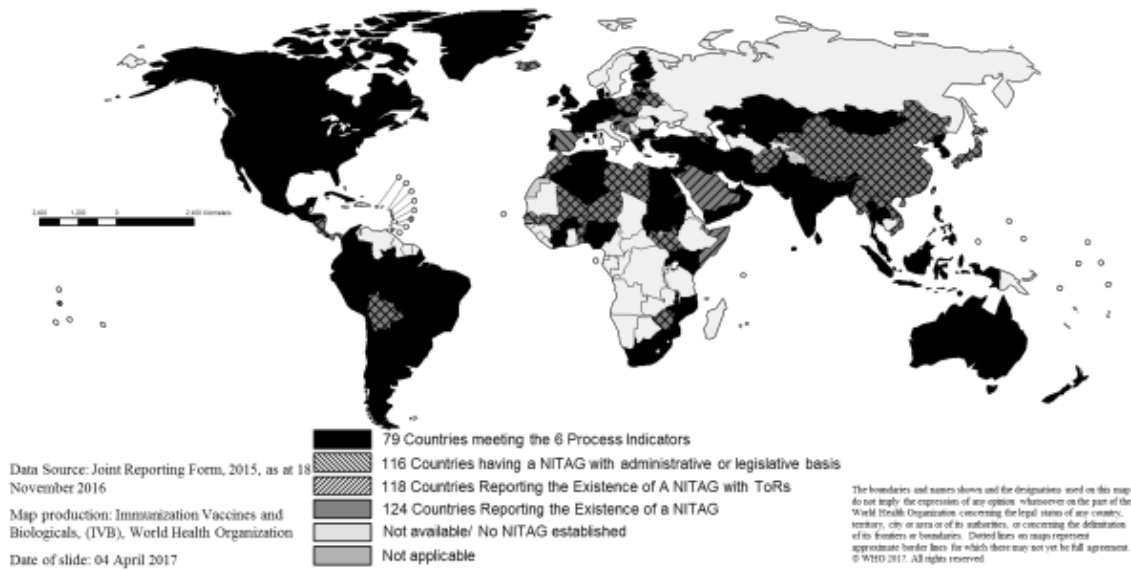
Figure 2 presents the 2010–2015 trajectory in the establishment of NITAGs. The trajectory through 2020 highlights the need for acceleration of progress to reach the GVAP NITAG target.

⁵ As at 18 November 2016, Member States that have yet to submit 2016 JRF data for 2015 include Albania, Libya, Monaco, and Poland. Albania has recently submitted JRF data but too late to be included in the current analysis.

⁶ Member States that have not completed the NITAG portion of JRF include Luxembourg, Sudan, and Tuvalu.

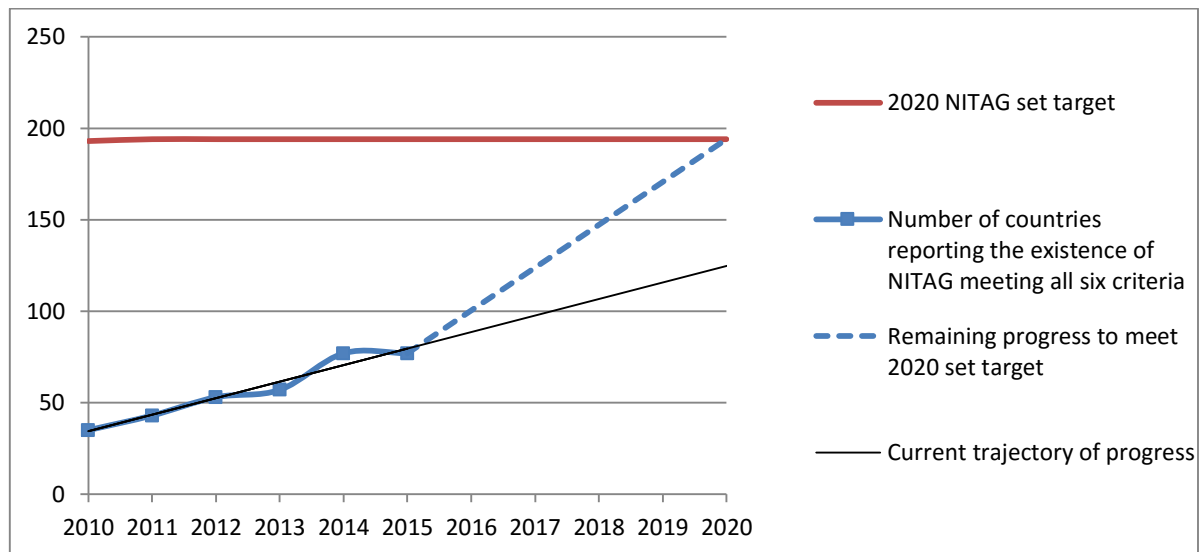
⁷ Luxembourg.

Figure 1: National Immunization Technical Advisory Groups in 2015



Source: WHO-UNICEF Joint Report Form, as of 18 November 2016

Figure 2: Time trend 2010–2015 in the establishment of NITAGs meeting all six process indicators, and remaining progress needed to reach 2020 target



Source: WHO/IVB Database, as of 18 November 2016

Table 1: NITAG characteristics at global level at by WHO region, 2015

Countries reporting/ WHO Member States	Indicator	OVERALL					
		AFR	AMR	EMR	EUR	SEAR	WPR
Existence of a NITAG	Number of countries	16	21	21	42	11	13
	% of countries	64%	60%	100%	79%	100%	48%
	% of the entire population covered	89%	94%	100%	66%	100%	99%
Existence of a NITAG with formal terms of reference	Number of countries	16	20	20	39	11	12
	% of countries	61%	57%	95%	74%	100%	44%
	% of the entire population covered	88%	94%	99%	60%	100%	99%
Existence of a NITAG with a legislative or administrative basis	Number of countries	16	19	19	39	11	12
	% of countries	60%	54%	90%	74%	100%	44%
	% of the entire population covered	88%	94%	93%	64%	100%	99%
Existence of a NITAG with >= five areas of expertise represented	Number of countries	16	19	19	41	10	10
	% of countries	59%	54%	90%	77%	91%	37%
	% of the entire population covered	86%	94%	93%	66%	100%	91%
Existence of a NITAG which met at least once a year	Number of countries	9	21	18	39	9	13
	% of countries	56%	60%	86%	74%	82%	48%
	% of the entire population covered	84%	94%	89%	57%	97%	99%
Existence of a NITAG for which the agenda and background documents distributed >= one week prior to meetings	Number of countries	11	19	18	40	11	11
	% of countries	57%	54%	86%	75%	100%	41%
	% of the entire population covered	85%	93%	94%	65%	100%	92%
Existence of a NITAG whose members required to disclose conflict of interest	Number of countries	13	15	17	30	9	9
	% of countries	48%	43%	81%	57%	82%	33%
	% of the entire population covered	65%	91%	96%	57%	96%	19%
Existence of a NITAG meeting all six criteria above	Number of countries	9	15	13	27	8	7
	% of countries	41%	43%	62%	51%	73%	26%
	% of the entire population covered	60%	91%	80%	51%	96%	12%

Source: WHO-UNICEF Joint Report Form, as of 18 November 2016

Interpretation

Notable progress was achieved between 2010 and 2015. In 2015, 116 (60%) Member States overall reported the existence of a NITAG with a formal legislative or administrative basis. In 2015, there were 79 Member States⁸ with a NITAG that met all six process indicators, including a total of 50 developing Member States. This is a 113% increase compared to 2010, when only 37 countries reported having a NITAG meeting all six process indicators. The global trend shows minimal progress, however, in the number of countries meeting the six process indicators between 2014 and 2015. In 2015, 9 new countries⁹ met the six process indicators, while 10 countries dropped from the list¹⁰. The main cause of this drop is the fact that the NITAG did not meet in 2015 for nine of these countries.

In 2015, 16% of low-income countries, 38% of middle-income countries, and 59% of high-income countries reported having a NITAG meeting all six process indicators. Overall, 60% of the global population live in a country with a NITAG that meets all six process indicators.

Table 2: NITAG status per income-level from 2010 to 2015

Year	2010			2015			% increase 2010-2015 all countries
	LIC	MIC	HIC	LIC	MIC	HIC	
Income-level							
% of countries included in the analysis per income-level (N)	100 (30)	96 (101)	95 (53)	100 (31)	100 (105)	100 (56)	
Existence of a NITAG with a legislative or administrative basis % of countries (N)	07 (2)	41 (43)	59 (33)	45 (14)	60 (63)	70 (39)	49%
Existence of a NITAG meeting all six criteria % of countries (N)	03 (1)	19 (20)	38 (21)	16 (5)	39 (41)	59 (33)	88%

Source : WHO-UNICEF Joint Report Form, as of 18 November 2016 and World Bank Income classification as of March 2017 (classification not available for Niue and Cook Islands).

In 2010, there were 30 low income countries as South Sudan became a WHO Member State in 2011.

⁸ Algeria, Andorra, Argentina, Australia, Azerbaijan, Bahrain, Bangladesh, Belgium, Brazil, Bulgaria, Burkina Faso, Canada, Chile, Colombia, Côte d'Ivoire, Cuba, Czech Republic, Democratic People's Republic of Korea, Denmark, Ecuador, Egypt, El Salvador, Estonia, Finland, France, Germany, Greece, Guatemala, Honduras, India, Indonesia, Iran (Islamic Republic of), Iraq, Ireland, Israel, Jordan, Kazakhstan, Kenya, Lithuania, Luxembourg, Malawi, Malaysia, Maldives, Malta, Mexico, Monaco, Mongolia, Mozambique, Netherlands, New Zealand, Nigeria, Oman, Pakistan, Paraguay, Peru, Philippines, Portugal, Qatar, Republic of Korea, Republic of Moldova, Singapore, Slovakia, Slovenia, South Africa, Sri Lanka, Sudan, Switzerland, Syrian Arab Republic, Thailand, Timor-Leste, Tunisia, Turkey, Uganda, United Arab Emirates, United Kingdom, United States of America, Uruguay, Uzbekistan, Yemen.

⁹ These nine countries are Bulgaria, Burkina Faso, Egypt, Malawi, Mozambique, Nigeria, Timor-Leste, Uganda and United Arab Emirates. Data from Greece was not included in the last report but did report (late) that it met the six process indicators.

¹⁰ The 10 countries that dropped from the list are Afghanistan, Armenia, Benin, Bhutan, Bolivia, Djibouti, Kyrgyzstan, Morocco, Nepal and Senegal.

The South-East Asia Region (where all countries have now established a NITAG) had the highest proportion of Member States reporting the existence of a NITAG that met all six process indicators (73%) and the African Region the lowest (45%). Nevertheless, remarkable progress was made in the African Region between 2014 and 2015, multiplying by more than two the total population living in a country having a NITAG meeting the six process indicators (from 20% to 45%). The South-East Asia Region also had the greatest percentage (100%) of Member States that had a NITAG based on a formal legislative decree. Percentages in the other regions were 34% (African Region), 74% (European Region), 90% (Eastern Mediterranean Region), 44% (Western Pacific Region) and 54% (Region of the Americas) – these two latter regions being affected by a substantial number of small Member States. Mandatory declaration of conflict of interest (COI) of NITAG members was the main limiting factor for Member States to meet the criteria for having a fully functional NITAG (i.e., met all six process indicators); in 2015, of the 45 countries which had a NITAG but did not meet the six indicators, 31 of these countries lacked a mandatory COI declaration. The lack of COI declaration can be a problem of both history and culture.

By end 2015, of the 70 countries globally that did not report the existence of a NITAG, 31 were located in the African Region and 23 were small countries (less than 1 million total population) located in the Western Pacific Region and the Region of the Americas. Globally, there are 40 small countries with populations of less than 1 million and 28 (70%) have no NITAG; the proportion of small countries with no NITAG varies by region: AFR (5/5, 100%), AMR (10/11, 91%), EMR (0/1, 0%), EUR (1/7, 14%), SEAR (0/2, 0%), WPR (12/14, 86%). Given limited technical capacity and resources in some of the small countries, it may not be necessary or possible to establish NITAGs in all of these countries (e.g., small island countries) and it makes more sense for countries to form and rely on subregional networks/NITAGs to fit their needs or develop relationships with a neighbouring NITAG as Monaco has done with France. Additionally, the finding that almost 40% of high-income countries do not meet criteria for having a functional NITAG does not necessarily mean that they are lacking an acceptable system for evidence-based vaccine decision making, given the country context (e.g., Norway with an advisory body embedded in their public health infrastructure). However, in these countries assessment of how well their process meets NITAG evaluation criteria has not occurred yet.

5. Issues and challenges faced by countries establishing or strengthening a NITAG

NITAGs are effective only if they are country-owned and given recognition as an expert advisory body. It is important for NITAGs to have the ability to access local resources to help prepare for sessions and reviews (e.g., access local surveillance data and outbreak investigations). However, the NITAG and work groups also need to weigh options based on resources and need, for example. Rather, existing systematic reviews or data from neighbouring countries can sometimes be used for evidence-based decision making (if possible to access that data); in addition, the global WHO contribution through the work of SAGE and other advisory groups can also be an important resource. However, there are still big gaps in vaccine preventable disease data in some regions that need to be filled to ensure local NITAGs have quality local evidence upon which to base decisions (1). There is no need for NITAGs to repeat good quality recently conducted vaccine safety and effectiveness systematic reviews.

Issues and challenges faced by countries presented in Table 3 come from regional reports and two literature searches on NITAG conducted on Pubmed and Sciencedirect databases. Twenty-one articles were considered for the purpose of this section (2-22).

Of note, most challenges faced by multiple NITAGs globally; those more specific to particular regions are cited as so.

Enabling factors and opportunities for NITAG establishment and strengthening include:

1. building on existing polio advisory committees;
2. collaborating with relevant vaccine initiatives: Rotavirus Accelerated Vaccine Introduction Network (RAVIN), Partnership for Influenza Vaccine Introduction (PIVI);
3. increasing partnerships with local and regional organizations (WAHO);
4. diversifying sources of funding for NITAG support;
5. supporting the secretariat functionality of the global and regional NITAG networks as platforms for sharing resources, best practices, experiences for providing peer-to-peer technical assistance;
6. continuing and further facilitating the sharing of expertise through the visit of members of newly established NITAG to experienced ones;
7. assessing the feasibility and functionality for small states and territories of different models such as subregional networks or partnerships with neighbouring NITAG to address the availability of expertise issue (2-4). As an example, the successful establishment of the sub-regional network of the Caribbean helped bringing a more formalized approach to reviewing and considering evidence for immunization decision-making. This built on a local history and culture of collaborative work. Monaco works with France's NITAG. One needs to ensure these models actually result in local small countries using the subregional or other country's NITAG advice.

Table 3: Challenges to NITAG establishment and functioning

Challenge	Comment
<i>Challenge to NITAG establishment</i>	
Lack of political commitment to establish a NITAG	Countries need to take an active role in establishing and maintaining NITAGs and to investigate innovative mechanisms to sustain funding for NITAGs.
Low awareness on NITAG role by national authorities	Confusion with other existing bodies (ICC, Expanded Programme on Immunization (EPI), Polio committees, health technology assessment (HTA) agencies), mostly in WPR and AFR, where vertical committees are numerous. Fear of delegating power to an independent group of experts which would undermine national authority, challenge prerogatives, and conflict with priorities.
Lack of financial resources	Insufficient and non-sustainable funding and resources in LMIC. In EUR, the sustainability of recently-established MIC NITAGs and of Gavi graduating countries' NITAGs is questioned due to the limited funds available for support at the regional office. In AMR, regional and income-level disparities in countries' access to donor subsidies and pooled procurement mechanisms.
Insufficient support to national authorities	Need to sustain focal points in all WHO regions. Particularly critical in regions with a high proportion of MIC considering the very limited financial support available for NITAG activities in these countries. In EMR, Regional Office supported NITAG activities and follow ups could not be carried out to the extent required, while previously EMRO was very active in this area when a WHO NITAG focal point was in place at the Regional Office. In EUR, concerns that without continuing WHO and partners' support, NITAGs established 1-3 years ago may stop functioning; recently-established NITAG have not yet acquired the visibility and credibility for sustained funding.

<p>Lack of availability of qualified human resources</p>	<p>Time is the major constraint for qualified human resources to serve in the committees</p> <p>Scarcity of trained staff (local practitioners and researchers) to serve in the NITAG and NITAG Secretariat of small-population Island Nation-States and Territories is a challenge because immunization programs in these settings often cannot draw sufficient expertise from to build a committee.</p> <p>In AMR, limited technical capacity in remaining countries to generate and use evidence in future priority-setting and decision making processes.</p> <p>NITAGs strength resides in their multidisciplinary composition. But at the same time it is necessary that all members understand immunisation issues. Participation in vaccinology trainings remains slow</p>
<p>Political turmoil</p>	<p>Difficulty in NITAG establishment and function due to civil unrest, humanitarian crises that are not short term – guidance from WHO is coming but not yet available</p>
<p>Challenge to NITAG functioning</p>	
<p>Lack of NITAG operating procedures</p>	<p>Most AFR NITAGs, some WPR NITAG and some SEAR NITAG lack standards operating procedures to function. Documentation of NITAG work also limited.</p>
<p>Lack of the systematic declaration of conflicts of interest</p>	<p>Challenge in understanding the concept of conflict of interest has been reported globally. The absence of systematic declaration of interests by core members is problematic in many countries due to historical and cultural influences.</p> <p>The transparent process under which declarations should be revealed, the management of conflicts and the availability of related tools is detailed in a guidance document recently published by AMP.</p>
<p>Lack of importance given to defining annual work plans and agendas</p>	<p>Partners’ support to countries where NITAG work plans and agendas have not been defined is all the more challenging.</p>
<p>Lack of health authorities’ understanding of NITAG institutional independence</p>	<p>The philosophy of using an evidence-based process for making recommendations and of valuing the independence of national experts are foreign concepts in many cultures and can be further nourished by authorities’ fear of members’ lack of independence from other interest groups.</p> <p>National authorities have showed difficulty in understanding how compatible the concepts of NITAG independence from the government and of NITAG integration in the decision-system are.</p>

Lack of access to necessary data	Lack of systems in place to generate country-specific data on epidemiology, disease burden, cost-effectiveness. (eg. Gap in information on pneumococcal serotype distribution in Africa). In SEAR and WPR, lack of local data is further challenged by difficulty in accessing neighbouring, regional and global data. In addition to access to data, time and resources needed for critical review of the evidence are not always available.
Language issues	Access to Russian publications either originally published in Russian or translated after initial publication in another language is rare which constitutes a major barrier to NITAG functioning in Eastern EUR countries. For example, most systematic reviews collected in the SYSVAC database (a database of systematic reviews on vaccines and immunization at http://immunisation.hpru.nihr.ac.uk/sysvac) are in English. Prioritization of publications/data to be translated need to be determined based on countries' feedbacks.
Lack of public information about NITAGs and their work processes	Lack of report of a codified and systematic process used by NITAG for collecting and evaluating data. When reported, these processes are not always as detailed, structured and transparent as for other medicines. It is difficult to find full documentation of the topics addressed by NITAGs, including the evidence used and whether (and how) it was assessed. Several NITAGs remained only focused on the introduction of new vaccines and efforts should be made to expand their scope to reviewing the use and impact and optimizing strategies for already introduced/long standing vaccines; optimizing the use of existing vaccines and strengthening national immunization programmes.
Lack of communication between NITAG members and national decision-makers	Communication channels are not clearly defined for the MoH consideration of NITAG recommendations. Countries have called for best practice guidelines on communication and NITAG integration in the national decision-making system.

Lack of ability to influence and change policy and practice	Lack of ability to influence and change policy and practice was reported as a challenge globally, particularly in LMIC (13). Linked to the country's policy environment and legislation, other influencing factors include: 1) Lack of quantity of connections between NITAG members and decision-makers, which appears to some to contradict the concept of NITAG autonomy/independence from the government. Further advocacy is required in this regard. However, NITAG may have partners such as WHO country and regional offices, GAVI with good connections with MoH, which can facilitate the consideration of NITAG recommendations and policy change. 2) Lack of quality of connections: NITAG need to invest time and efforts in the long-run to build these connections. Staff turnover in the political arena may represent another obstacle. 3) Lack of capacity (expertise and when present, its availability) to conduct NITAG work 4) Lack of reputation which is also built in the long run. Opportunities to build on SAGE reputation have not been explored enough. The US-CDC is in the process of evaluating NITAG integration and decision-making in different WHO regions.
---	--

6. Partners roles and investments in supporting countries to establish and strengthen NITAGs

The major technical partners in NITAG strengthening are WHO and AMP-HPID which hosted the Supporting Independent Immunization and Vaccine Advisory Committees (SIVAC) Initiative. Efforts began in 2006, when SAGE recommended that WHO provide technical advice to governments on evidence-based decision-making, priority setting, and the introduction of new vaccines. WHO assumed the work of supporting countries through regional officers in each WHO region, often in conjunction with work on new and underutilized vaccine introduction, coordinated by a focal point at headquarters. In 2008, the SIVAC Initiative was launched to support the creation and strengthening of NITAGs in low and middle income countries. From 2009-2013, SIVAC was a partnership between AMP, focusing on the AFR and SEAR, and IVI on the WPR and EUR. In 2012 based on the work of SIVAC, the AMP-HPID Center¹¹ was designated as a WHO Collaborating Center for evidence-informed immunization policy-making with the main objectives to: 1) Contribute to WHO promotion of a systematic use of evidence-informed policy-making processes in immunization; 2) Collaborate with WHO on scaling-up initiatives to improve the use of evidence informed policy-making processes in immunization, in particular through the creation and strengthening of NITAGs; 3) Facilitate the exchange of information within the immunization community (including NITAGs) in order to foster south-south, north-south and north-north collaborations.

Partners' areas of support include: conducting high level advocacy to national authorities and funders; providing guidance in NITAG establishment processes and optimum functioning; dissemination of global and regional recommendations; facilitating NITAG capacity building (organisation of trainings, study tours, attendance to specific course i.e., vaccinology courses, literature search and appraisal; development of tools); supporting NITAGs functioning (technical assistance in development of NITAGs documents including evidence-informed recommendations); providing financial resources for NITAGs operations. Although each partner provides technical support according to its comparative advantage, it must be emphasized that assistance to NITAGs is a collaborative effort operating within the framework of the NITAG Group of Partners coordinated by WHO HQ. This group is composed of the NITAGs 'main partners, providing continuous assistance to NITAGs. AMP-HPID and WHO have led the way in developing and testing strategies and resources to help countries improve country ownership of immunization policy through the establishment and strengthening of a NITAG. Details on their contributions are given in the next section.

The main partners providing financial support are the Bill and Melinda Gates Foundation (BMGF) (through the SIVAC Initiative), GAVI, and U.S. CDC (mainly for WHO's NITAG work). In addition a few other sources of funds have been used to a limited extent to fund NITAG establishment and strengthening work such as WHO assessed contributions [core WHO funds], WAHO [for West African countries]; USAID, and some disease specific initiatives (e.g., Partnership for Influenza Vaccine Introduction (PIVI)). Overall funding has been quite limited and hard to secure.

Other partners have also contributed to the development of tools and other resources. For example, from 2009 the U.S. CDC began collaborating with WHO and SIVAC in the development and use of

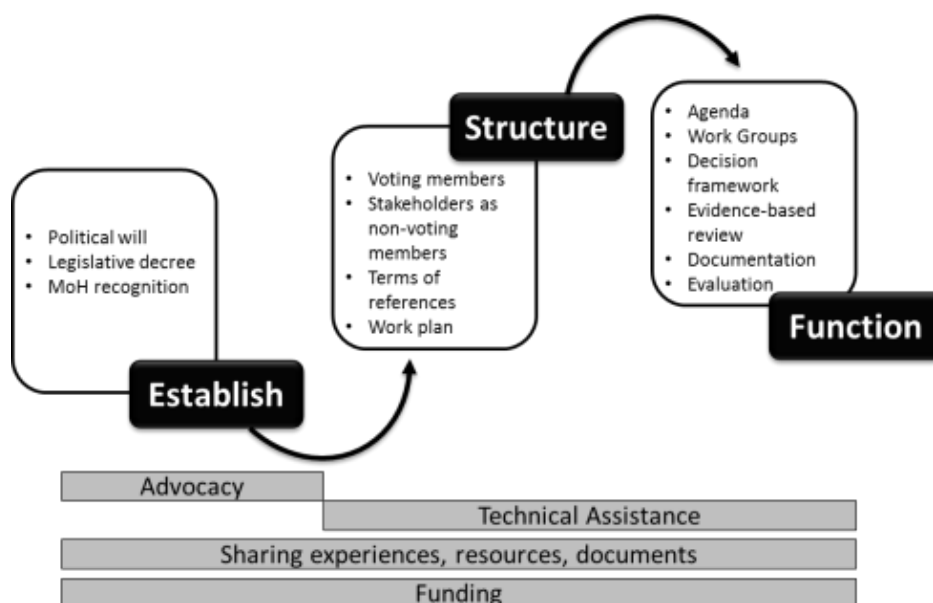
¹¹ AMP-HPID website is accessible at: <http://amp-vaccinology.org/HPID>

training materials and provision of technical assistance and resources for variety of activities. The West Africa Health Organization (WAHO) has assisted AMP-HPID with activities in West Africa. Several partners, including the European Centre for Disease Control and Prevention (ECDC), United States Agency for International Development (USAID), and National Institutes of Health (NIH)- Fogarty International Center, and the Sabin Vaccine Institute have contributed through the development of specific tools as described below. Finally, vertical disease specific initiatives such as the Rotavirus Accelerated Vaccine Introduction Network (RAVIN), and PIVI, have recently shown interest in NITAG strengthening.

Partner strategies

The process of developing a functional NITAG can be considered in terms of three stages as depicted in Figure 3. Throughout this continuum, partners have systematically and thoughtfully consulted with countries to understand the barriers and enablers for progressing through each phase. It was recognized early on that one approach does not fit all countries. A variety of strategies and resources have been developed, used in many countries, and iteratively adapted according to national and regional contexts. Access to funding to support the partner inputs is critical.

Figure 3: Three stages to outline the process of developing a functional NITAG.



Establish.

WHO and SIVAC have supported many countries interested in establishing a NITAG by advocating with the government. Such advocacy aims to raise awareness of the value of and generate political will for a NITAG, develop legislative underpinning for political sustainability, and foster recognition of the NITAG by the MoH. Because this is a country driven process, SIVAC and WHO Regional focal points have recognized the importance of ‘thoughtful listening’ and respectful consultation to gently guide rather than pro-actively lead. In this way, partners understand the contextual situation, political environment, and institutional stability, all of which affect the trajectory of NITAG establishment. This phase can be lengthy for several reasons. First, there are key differences

between support for NITAG creation and typical support to EPI, for example improving cold chain, access to vaccination, or disease surveillance. NITAG creation builds a new program 'from scratch', while other support usually builds on some sort of existing infrastructure. Secondly, the concept of a committee independent from the government is not familiar in many cultures. For example, some health country officials expressed that opinion that a committee not chaired by the EPI manager would not be recognized. Some have said building a NITAG is akin to putting a little bit of democracy into the policy process. As a result, helping countries by simply providing guidelines would not be adequate for NITAG establishment.

Advocacy varies by region and by country, but a common feature is that it takes time. For example, two AFR countries established their NITAGs in one year, most took 2 to 3 years and one did not establish until 8 years after the initial engagement. In the African region, the advocacy by AFRO and SIVAC, and of WAHO in francophone West Africa, takes the form of: 1) letters and visits to the MoH; 2) support to EPI to organize meeting of immunization stakeholders; 3) participation and presentation at EPI meetings; 4) side meetings with EPI managers and partners; and 4) invitations a NITAG orientation meeting. In EMR, early on the Regional Director sent letters to Ministers of Health emphasizing importance of establishing and strengthening NITAGs. The European region uses similar strategies, sometimes involving the Regional Director if the country has particular concerns. In addition, NITAG sessions are held during the regional meetings for Immunization Programme Managers. A key advocacy tool is the inclusion of NITAG establishment and strengthening as one of the main strategic objectives of European Vaccine Action Plan for 2015-2020, which was endorsed by all WHO EUR Member States at WHO Regional Committee Meeting in September 2014.

Globally, the most recent officially established NITAG is the NITAG in Haiti (AMR), as marked by an inauguration ceremony of the NITAG on 8 March 2017. Prominence was given to highlight the terms of reference of the NITAG, diversity of membership on the advisory group, and keen interest calling for the first meeting to be organized rapidly in order to address pressing public health vaccination-related concerns.

Structure.

Once the creation of a NITAG has legal status, it should be structured for maximum effect according to best practices described in the WHO guidelines. AMP-HPID took the lead for this phase and actively involved WHO and CDC in the development and delivery of workshops, trainings, and resources (See Table 4 and Table 5). The activities aim to convey the value of a committee independent of the EPI and composed of a broad range of expertise, to assist in the identification and involvement of immunization stakeholders, and to help countries develop written terms of reference, including conflict of interest assessment and management. AMP-HPID have developed a range of resources including simple, practical templates that committees can adapt to their context; workshop guides for facilitators and materials for participants; and guides for complex activities such as mapping immunization stakeholders and determining their role in the development of immunization policy. These materials have been used both in countries establishing new NITAGs and in those with existing committees. Many countries with existing committees decided to revise the structure after considering the WHO guidance. Examples include the Lao People's Democratic Republic's committee that recently stated the need to replace purely administrative members with technical experts and the Afghanistan NITAG that announced plans to totally revamp their

committee. The format of the workshops includes didactic and participatory learning. In general, training materials have been developed for a particular target audience and then iteratively revised for other countries and contexts. For example, a pre-workshop needs assessment for training in one region showed particular interest in developing a charter for their NITAG. To address this, examples of charters and templates were used by participants in group work.

Functioning.

A well-functioning NITAG should be able to complete both management functions and technical activities. To enable the NITAG to function efficiently, the NITAG secretariat and members need to develop a work plan that reflects relevant immunization policy issues with input from the EPI and other immunization stakeholders, organizing and setting the agenda for each meeting, and recruiting new members as terms expire. Technical activities especially led by the NITAG chair include developing a decision framework, conducting evidence based reviews possibly through technical work groups, and making evidence based recommendations. Another important management function is documentation, for example of the decision framework and the recommendations and notes showing the evidence base. Finally, NITAGs should be able to evaluate their work and impact.

All partners have been involved in this phase and in a variety of ways. WHO, AMP-HPID and US CDC have provided technical assistance, training, and provision of resources as shown in Table 4 and Table 5. As with workshops on structure, there have multiple formats including practical case studies adapted to the target audience. Often members of well-established NITAGs have participated in trainings; there have been consistent comments about the value of such experience sharing. Partners have found other opportunities for sharing among countries through the development of web-based platforms and networks. To provide such interactions, the web-based NRC, a GNN, a SEAR NITAG network and a European Union NITAG network (VENICE) were established.

Many tools to promote evidence-based decision making on new vaccine introduction have been developed based on needs assessment. Acknowledging that one size fits all approach would not work, partners' assessments followed an iterative process and tools adapted to context. One example is ProVac which <http://amp-vaccinology.org/activity/provac-iwg> was developed by PAHO in response to Latin American country requests for technical support in the integration of economic decisions on new vaccine introduction. As of 2017, 15 countries in the region had completed more than 30 country-led analyses on the costs, impact and cost-effectiveness of new vaccine introduction¹². The PROVAC International Working Group was created to extend ProVac to other WHO regions. PAHO also developed UNIVAC, a vaccine predictive impact and cost-effectiveness model that allows users to customize structure to a policy question about multiple vaccines.

Web tools are also being developed under the WHO project of optimizing NIP schedules and with the SMART Vaccines 2.0. In development by the US National Institute of Health (NIH)-Fogarty International Center, this decision-making tool will represent the dynamic, multidimensional nature of the process of decision-making. Input data goes beyond the standard data used in cost-effectiveness analyses and can capture policy, politics, and feasibility. The tool is designed to rank

¹² Andrus JK, Walker DG. Expanding the Evidence Base to Inform Vaccine Introduction: Program Costing and Cost-effectiveness Analyses. Volume 33, Supplement 1, Pages A1-A254. <http://www.sciencedirect.com/science/journal/0264410X/33/supp/S1>.

priorities and not answer a specific vaccine decision-making question. The adapted version SMART Vaccines 2.0 may be useful for NITAG and may be piloted in a country for this purpose.

The immunization dashboard is being used by USAID and contains a section on diagnostic indicators including GVAP indicators, stratified by the 24 USAID priority countries. A NITAG indicator may be added to show a grade for the country's NITAG based on the six indicators. The dashboard will be updated annually using information from JRF and WHO.

The European Centre for Disease Prevention and Control (ECDC; at <http://ecdc.europa.eu/en/Pages/home.aspx>) works in partnership with national health protection bodies across Europe and collects Europe's health knowledge to develop authoritative scientific opinions on issues related to vaccine preventable diseases. The Robert Koch Institute in Germany has convened a series of meetings to strengthen evidence-based decision-making by NITAGs and has engaged in the strengthening of NITAG processes. Other groups, such as the Johns Hopkins Bloomberg School of Public Health has been funded by Gavi for various diseases specific initiatives.

Funding.

Clearly, funding is needed throughout the entire process of NITAG development. SIVAC has been supported from 2009-2017 by the BMGF with complementary funds from Gavi in 2015-2016. CDC provides funds to WHO HQ to support NITAG members from selected countries to attend the SAGE or regional TAGs meetings and WHO country offices for NITAG strengthening activities awarded through CDC small grants program. In addition, Gavi offered countries two funding sources for NITAG support through Health System and Immunization Strengthening (HSIS) and Tailored Country Assistance (TCA) grants, but support for NITAGs has not been prioritized within these opportunities. In 2016, however, Joint Appraisals in 16 countries (13 in the AFR) eligible countries identified and prioritized NITAG support in their TCA requests.

Table 4: Activities conducted/supported by partners by three phases of NITAG development, 2009-2016 (based on information received from partners)

	2009	2010	2011	2012	2013	2014	2015	2016	2009-2016 total # of countries
Phase I: Establish									
Advocacy meetings with national authorities or informal engagements ¹									
Phase II: Structure									
Workshop on Establishment and mode of operations of an effective NITAG ²	1	13	4	2	3	2	6	6	37
Workshop on Analysis of immunization in the context of health systems and policy decision-making									
Phase III: Function									
Workshop on Evidence-based decision making ³					15	11	5	7	38
Training of NITAG facilitators ⁴							5	0	5
Sponsored attendance at Vaccinology course ⁵			4	5			3	3	15
Sponsored attendance at SAGE ⁶							16	20	36
Invitation to Regional and subregional meetings ⁷									
Sponsored visit to other NITAGs ⁸		3	3		1	3	6	2	18
Evaluation or needs assessment tools ⁹		3				1	1	11	16

¹Advocacy

Formal and informal activities were carried out throughout in 36 countries supported by SIVAC-AMP and -IVI, 10 countries in EUR, many countries in PAHO. The number of countries is not captured in the table.

²Orientation workshops

2009 National workshop in Nepal [WHO, SIVAC-IVI, CDC]

2010 Regional workshop including Belarus, Moldova, Ukraine [WHO, SIVAC-IVI, CDC]; Regional workshop including Mongolia, Vietnam, Philippines, Cambodia, Lao, Fiji, Papua New Guinea, South Korea, Hong Kong, China [WHO, SIVAC-IVI]

2011 Regional workshop including Kazakhstan, Kyrgyzstan, Uzbekistan; National workshop in Bhutan [WHO, SIVAC-IVI, CDC]

2012 National workshops in Myanmar and Mongolia [WHO, SIVAC-IVI]

2013 National workshops in Benin, Senegal, Maldives [WHO, SIVAC-AMP]

2014 National workshops in Vietnam, Kenya [WHO, SIVAC-IVI-AMP]

2015 National workshops in Cote d'Ivoire, Uganda, Burkina Faso, Nigeria, Malawi, Timor Leste [WHO, SIVAC-AMP]

2016 National workshops in South Sudan, Kenya, Ethiopia, Zimbabwe, Tanzania, Zambia [WHO, SIVAC-AMP]

³Evidence-based decision-making

2013 Regional workshop including Cote d'Ivoire, Senegal, Benin [WHO, SIVAC-AMP]; Two regional workshop including Albania, Bosnia and Herzegovina, Hungary, Montenegro, Romania, Serbia, Armenia, Azerbaijan, Kazakhstan, Kyrgyzstan, Ukraine, Uzbekistan [WHO, CDC, NITAGs from Germany, Netherlands, and the United Kingdom]

2014 Regional workshop: Kenya, Uganda, South Sudan, Ethiopia, Zambia [SIVAC-AMP, WHO], Regional workshop: Bulgaria, Estonia, Hungary, Latvia, Lithuania [WHO, CDC]; Workshop with special focus on Health Economics in decision-making: Tunisia [SIVAC-AMP, WHO]

2015 National workshops in Benin, Nigeria [WHO, SIVAC-AMP]; National workshop with special focus on evidence assessment using GRADE for Kenya [SIVAC-AMP, WHO]; Regional workshop with special focus on literature search and assessment of articles including Benin, Senegal [WHO, SIVAC-AMP]

2016 National workshops in Uganda, Burkina Faso [WHO,SIVAC-AMP]; Vietnam [WHO, CDC]; Multi-country workshop with special focus on Health Economics in decision-making including Cote d'Ivoire, Burkina Faso, Senegal, Benin [WHO, SIVAC-AMP]

2004-2016 PAHO's ProVac Initiative has hosted a number of regional trainings on specific vaccines, assess local data availability and quality to address the policy question and, where relevant, understand and use modelling techniques to estimate the projected costs, health benefits and cost-effectiveness of the proposed vaccination strategy. The number of countries is not captured in the table.

⁴Training of NITAG facilitators

2015 Multi-country workshop including Mozambique, Kenya, Cote d'Ivoire, Nigeria, India [WHO, SIVAC-AMP]

⁵Vaccinology courses (Advanced Course of Vaccinology (ADVAC), Vaccines for Africa Initiative (VACFA), Charite-Berlin, WHO AFRO, or International Vaccine Institute (IVI)) (of course many more NITAG members or staff from NITAG secretariats have attended vaccinology courses and some courses such as ADVAC give some priority to the participation of such participants and offer some grants to support participation of trainees from developing countries)

2011 Indonesia, Vietnam, Nepal, Mongolia

2012 Indonesia, Kazakhstan, Kyrgyzstan, Mongolia, Vietnam

2015 Burkina Faso, Nigeria, Kenya

⁶Study visit to SAGE meeting

2015 Afghanistan, Barbados, Bulgaria, Cote d'Ivoire, Croatia, Mozambique, Oman, Philippines, Republic of Moldova, South Africa, Sri Lanka, Suriname, Thailand, Timore-Leste, Turkey, Uganda [WHO, SIVAC-AMP]

2016 Albania, Armenia, Belarus, Belgium, Bhutan, Burkina Faso, China, Georgia, Germany, Indonesia, Malawi, Maldives, Papua New Guinea, Panama, Philippines, Senegal, South Sudan, Uganda, Viet Nam, Zimbabwe, [WHO, SIVAC-AMP]

⁷Participation in regional and subregional meetings.

The number of countries is not captured in the table. Over the recent years, NITAG Chairs and secretariats have been invited to join at immunization managers meetings and at regional TAG meetings. This has also resulted in opportunities for regional NITAG meetings in the context of these other meetings. As an example between 2009-2016--NITAGs from 15 low and middle-income countries in EUR attended each ETAGE meeting and NITAGs in EUR countries were invited to attend Immunization Programme Managers Meetings and other annual regional meetings on immunization and introduction of new vaccines. NITAG chairs from AMR countries participate in the Regional TAG on VPD. NITAG chairs participate in the annual subregional meeting of

Caribbean English-Speaking immunization programs to review and consider evidence for immunization. NITAG chairs and secretariat have also been invited to join regional TAG meetings and immunization manager meetings in the other WHO regions.

⁸Study visit to other NITAGs

2010 Tunisia, Lebanon, Cote d'Ivoire [SIVAC-AMP, WHO, NITAGs of Quebec and France]

2011 Mongolia, Vietnam, Indonesia [SIVAC-IVI, WHO, NITAGs of New Zealand and Australia]

2013 Nepal [SIVAC-AMP, WHO, NITAG of Australia]

2014 Cote d'Ivoire, Senegal, Vietnam [SIVAC-AMP, WHO, NITAGs of France and South Korea]

2015 Kenya, DRC, Armenia, Moldova [SIVAC-AMP, WHO, NITAGs of South Africa, Belgium, USA, UK, France], Peru, DRC [WHO, CDC and NITAG of USA]; Belarus, Georgia [WHO, NITAG of the Netherlands]

2016 Albania [WHO, NITAG of UNK]; China [WHO, SIVAC-AMP, CDC and NITAG of USA]

Not captured in the table are regular visits to other NITAGs facilitated by PAHO

⁹Evaluations

2014 Cote d'Ivoire NITAG conducted self-evaluation using country developed tool

2014 Pilot evaluations in Mongolia and Nepal [WHO]

2015 SIVAC evaluated Armenian NITAG, using SIVAC tool [WHO/SIVAC-AMP]

2016 EURO conducted needs assessment of 10 NITAGs, using regionally developed tool; SIVAC evaluated Moldovan NITAG, using SIVAC tool [WHO/SIVAC-AMP]; SEARO conducted an assessment of all 11 countries' NITAGs to understand experiences with establishment, structure, process, function, operations, and sustainability of NITAGs in the region.

Table 5: Resources and platforms for NITAG establishment and strengthening

Although AMP-HPID (as a WHO collaborating centre) and WHO have led the way in developing and testing strategies and resources to help countries improve country ownership of immunization policy through the establishment and strengthening of a NITAG, other partners including U.S. CDC, Gavi, Sabin Foundation, RKI, ECDC, USAID, and NIH Fogarty Center have or are also contributing to development of tools and other resources. The main tools and resources for NITAG establishment and strengthening are outlined here.

Resources	Purpose	Access	Date of publication
Resources for NITAG Establishment			
Guidance Document for the development of a Concept Paper on the Establishment and Functioning of a NITAG	Builds on WHO guidance; it presents the key points to be addressed while developing a concept paper for the establishment of a NITAG.	http://www.nitag-resource.org/media-center/document/1256-guidance-document-for-the-development-of-a-concept-paper-on-the-establishment-and-functioning-of-a-national-immunization-technical-advisory-group?page=1&disease=0&document_type=55&topic=0&geographical_area=&country=0&sort=recent&keyword=0&author=0&source=0&document_language=0	2015
Guidelines for defining NITAG annual Work Plan	Make the most economical and effective use of resources, in order to ensure the development of high quality, evidence-informed recommendations	http://www.nitag-resource.org/media-center/document/698-guidelines-for-defining-nitag-annual-work-plan?page=2&disease=0&document_type=55&topic=0&geographical_area=&country=0&sort=recent&keyword=0&author=0&source=0&document_language=0	2013, revised 2015
Internal procedures manual	Provide templates to guide NITAG secretariat in setting up NITAG operating procedures	http://www.nitag-resource.org/media-center/document/844-drawing-up-the-nitag-s-internal-procedures-manual?page=1&disease=0&document_type=0&topic=0&country=0&keyword=0&author=0&source=0&document_language=0&search=internal+procedures+manual	2014, revised 2015
Training materials--Participants' guide, facilitators' packet, including content, instructions, and slide set.		http://www.nitag-resource.org/uploads/media/default/0001/03/3475dc79774b8cf5ed712cae93048c017e6c8281.pdf	2014 piloted, 2015 finalized

EMRO Guidelines for NITAGs			http://applications.emro.who.int/dsaf/emropub_2011_1272.pdf	2011	
Case studies for training materials	Guide countries on NITAG composition and operations, charter development, and technical issues.			2009, revised after every use/CDC	
Guidelines for the Prevention of Conflicts of Interest in NITAGs	Introduction to principles and provide guidance to implement Conflict of Interest management policy		http://www.nitag-resource.org/uploads/media/default/0001/04/e80de42a64ee6f017cc42996b34a0cbb6e056ff0.pdf	2015	
Resources for NITAG Strengthening					
Guidelines for setting up NITAG working groups; template Terms of Reference for working groups	Guide NITAG executive secretariat in considering the need for establishing a Working Group to gather and summarize data for the NITAG meetings.		http://www.nitag-resource.org/media-center/document/697-guidelines-for-setting-nitag-working-groups?page=2&disease=0&document_type=55&topic=0&geographical_area=&country=0&sort=recent&keyword=0&author=0&source=0&document_language=0	2013	
Step by step guidelines to issue evidence-informed recommendations by NITAGs	Present overview of the steps involved in the process of evidence-based recommendation development		http://www.nitag-resource.org/media-center/document/692-a-step-by-step-guideline-to-issue-evidence-informed-recommendations-by-nitags?page=2&disease=0&document_type=55&topic=0&geographical_area=&country=0&sort=recent&keyword=0&author=0&source=0&document_language=0	2013	
Training materials--Participants' guide, facilitators' packet, including content, instructions, and slide set.	Establishment and mode of operations of an effective NITAG available in English and French (Training 1)			2014 piloted, 2015 finalized	
	Analysis of immunization in the context of health systems and the policy decision-making process available in English and French (Training 2)				
	Technical and scientific capacities of NITAGs, evidence assessment methodologies and the development of evidence-informed recommendations available in English, French and Russian (Training 3)				
	Informing vaccine decision-making with economic evidence available in English and French (Training 4)				
			http://www.nitag-resource.org/uploads/media/default/0001/03/3475dc79774b8cf5ed712cae93048c017e6c8281.pdf		

<p>Recommendation Frameworks (in relation to Training 3)</p>	<p>Samples of recommendation frameworks for 5 vaccines i.e. Hepatitis B birth dose, Meningococcal A, Rotavirus, Rubella and Tetanus-Diphtheria. The samples of generic framework with elements and specific queries can be adapted by the NITAGs to develop their actual disease specific framework and provide specific queries for each element.</p> <p>Sample search process and results tables based on the above recommendation frameworks for Hepatitis B birth dose and Meningococcal A</p>	<p>http://www.nitag-resource.org/media-center/document/882-elements-to-consider-in-developing-a-framework-for-issuing-immunization-related-policy-recommendations?page=1&disease=0&document_type=56&topic=0&geographical_area=&country=0&sort=recent&keyword=0&author=0&source=0&document_language=0</p>	<p>2015</p>
<p>Sample of PICO formulation (in relation to Training 3)</p>	<p>Sample of PICO formulation, formulation of search strategies, selection of articles and results of evidence appraisal scoring done for 10 vaccines: HepB Birth dose, HPV, MR, yellow fever, Tetanus-Diphtheria, Pertussis, MenA, Rotav, Pneumococcal Vaccines, Streptococcal B</p>		<p>2015</p>
<p>Evidence to decision tools</p>	<p>Tools developed by the DECIDE collaboration</p>	<p>http://www.decide-collaboration.eu/</p>	
<p>SAGE guidance document</p>	<p>SAGE follows an evidence-based review process as outlined in the SAGE guidance document on evidence-based vaccine-related recommendations. The document was developed in cooperation with the methodology working group. The document will continue to be updated as necessary as the methodology for evidence based decision making evolves.</p>	<p>http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf?ua=1</p>	
<p>Framework for Prioritization of Vaccine Introductions</p>	<p>Generic tool that builds on several existing tools (SMART vaccine version 1.0, WHO's Making Fair Choices on Universal Health Coverage, Guidance on Priority Setting in Health) aiming at guiding NITAGs in the</p>	<p>Tool not yet available. Similar tools also being developed by WHO under the optimization of schedules project.</p>	<p>2015</p>

		selection of vaccines for prioritization in a systematic and transparent way			
Evolution Tool for National Immunization Technical Advisory Groups (NITAGs)	Provides guidance and templates on NITAG self-assessment, collection of data through various sources, and analysis of information and writing of evaluation report.		http://www.nitag-resource.org/media-center/document/1517-evaluation-tool-for-national-immunization-technical-advisory-groups-nitags?page=1&disease=0&document_type=0&topic=0&country=0&keyword=0&author=0&source=0&document_language=0&search=evaluation+tool	2016	
Technical briefs on Reference Management Software Tools Zotero and Mendeley (in relation to Training 3)	Provide a short training on the use of Zotero and Mendeley to help the user create a bibliography and improve reference management		http://www.nitag-resource.org/media-center/document/3463-mendeley-reference-manager?page=1&disease=0&document_type=0&topic=0&country=0&keyword=0&author=0&source=0&document_language=0&search=mendeley	2016	
Guidance Document on how NITAGs can address questions raised by Vaccine Hesitancy	Presents key areas to be explored by NITAGs to better address vaccine hesitancy such as best practices to ensure independence, involvement of CSOs in the process of developing recommendations or NITAG communication strategies.		http://www.euro.who.int/en/health-topics/disease-prevention/vaccines-and-immunization/publications/2016/best-practice-guidance-how-to-respond-to-vocal-vaccine-deniers-in-public-2016	2016	
NITAG Financing Guidelines	Provide a list of funding options for NITAGs, based on SIVAC lessons and analysis of current global immunization financing solutions		http://www.immunizationfinancing.org/	2017	
Cost effectiveness resources including PROVAC, TRIVAC, CERVIVAC (cost effectiveness models), COSTVAC (program for modeling costing), OLIVES (on-line data repository)	Strengthen national technical capacity to make evidence-based decisions on new vaccine introduction, focusing on economic evaluations.		www.provac-toolkit.com	2004	
Platforms					
NITAG Resource Center	The NITAG Resource Center (NITAG-RC) (www.nitag-resource.org) in English and French, has three main components: a “NITAG observatory” a digital Library” and a Center of Expertise that includes modules for new NITAG members.		http://www.nitag-resource.org/	2010, revised 2015	
NITAG Newsletter	A NITAG newsletter is published on a quarterly basis. 350 people have subscribed. It promotes the latest recommendations issued by NITAGs, useful technical and operational resources for NITAG members and informs of		http://www.nitag-resource.org/contact	2015	

	upcoming events. It also enables the dissemination of documents and guidelines produced by SIVAC or other technical partners such as the training catalogue or the evaluation tool.		
Glossary (English – French)	Given the increasing number of partners working in the NITAG field, it appeared important to develop a glossary to ensure consistency in documents / guidelines / activities / workshops / concept notes, etc. and translations	2016	
Global NITAG Network	Provide a global platform to facilitate and support NITAGs, to promote active exchange of information among members and other capacity building activities	2016	http://www.nitag-resource.org/news-and-events/news/79-first-meeting-of-the-global-network-of-nitags
Southeast Asia NITAG Network	Provide a regional platform to share data and technical resources, facilitate exchange of experiences, and standardize policies and procedures around NITAGs.	2016	http://www.searo.who.int/entity/immunization/documents/the_establishment_and_operation_of_nitag_groups_in_scar.pdf
PAHO National Immunization Technical Advisory Groups (NITAGs)	A resource group to focus on strengthening skills at national level to develop economic and health impact evidence to inform decision making, to improve country ownership and sustainability.		
PAHO Webinar	Leveraging an existing monthly webinar hosted by the Regional Network of Health Technology Assessments, this forum allows discussion on immunization policy topics and issues		http://www2.paho.org/hq/index.php?option=com_content&view=article&id=11581%3Apahos-role-in-health-technology-assessment-in-the-americas&catid=5870%3Assessment&Itemid=41685&lang=en

Challenges faced by partners

Establishment and Structure

1. Lack of awareness and support among broader global partners with respect to the value of NITAGs;
2. Lack of awareness of the difference between NITAG strengthening and other support to EPI;
3. NITAG work often involves starting from 'scratch' while other EPI support usually builds on and improves existing systems;
4. Lack of consistent messaging and support among partners. Need a global agreement for the national governance of NIP and NITAGs so that global and regional partners operate in a coordinated way.

Functioning

1. Challenges of human resources and securing technical staff focused on NITAG-related issues both within WHO and for critical partners supporting NITAG strengthening.
2. Changes in leadership at the country level often result in stalls in the process of partner support and the need to repeat training for new staff. The process is often one step forward, two steps back;
3. Unclear role of disease specific initiatives (PIVI and RAVIN) in NITAG strengthening to ensure country ownership;
4. Difficulty in monitoring the impact of partners' work. Process indicators are helpful, but do not capture functionality and integration;
5. Difficulty in NITAG function due to civil unrest, humanitarian crises that are not short term – guidance from WHO is coming but not yet available. This can affect ability of technical assistance from partners to meet with NITAGs and provide support;
6. Too small populations to be to have expertise, evidence and data for full NITAG function;
7. Inadequate access to evidence in language NITAG members can use e.g. lack materials in Russian and/or lack of quality vaccine preventable disease data relevant to country. This can affect how partners interact and share materials with NITAGs.

Funding

1. Platforms such as the NRC, GNN, and regional networks have been developed, but their sustainability can only be ensured if there is funding for core infrastructure.

Future plans

All WHO regions have committed to increase national advocacy for NITAGs and recognize the need to share technical resources through regional networks. Regions will invest in this direction and continue regional and sub-regional trainings and collaborate between members of well-functioning NITAGs with those of recently-established NITAGs; continue invitations to regional meetings; standardize policies and procedures across NITAGs; facilitate NITAGs toward written standard operating procedures and work plans, and promote the use of the NRC as the global resource center for vaccine related information. Interest in conducting NITAG evaluation is also commonly shared across regions with the aim of continuously improving NITAG functioning, quality of work processes

and integration in the decision-making system. All regions need to creatively address challenges faced by low population states – one size fits all solutions are unlikely to work.

Efforts are also going forward towards investing in NITAG integration in decision-making system and innovating in policy making processes to be more cross-cutting across the health sector and supportive of integrated policy making.

Regarding funding, regions have started to tap into different resources (e.g., Gavi, Health System Strengthening (HSS)). Identifying funding and candidates for NITAG focal points in regions lacking one is particularly critical.

CDC will continue to support WHO and host country delegations to ACIP meetings. There are recently funded projects and ongoing CDC efforts to: pilot experiential learning by supporting a mentor to engage with a NITAG for 9-12 months around a specific policy question; document positive deviance on NITAG integration in the policy dialogue in Argentina, Jordan, and other countries; develop a maturity model of key milestones for sustainable NITAG development; identify contextual mechanisms developed by countries for maintaining polio assets by linkage with NITAGs; and update published systematic review of criteria for country decision-making.

WHO will further engage in the strengthening of NITAGs, e.g. by inviting selected NITAG chairs and secretariats to attend the SAGE meetings.

7. Summary and Way forward

The 2015 data shows slight progress in the establishment of new NITAGs; however, there is a relative stagnation on the strengthening of NITAGs. While the time-trend data shown in Figure 2 should not be over-interpreted, the trend is clear: the GVAP target for all countries to have a NITAG will not be met by 2020 through current activities. Although there has been overall positive progress in NITAG strengthening during the last five years, the progress has been uneven, and it is evident that there are weaknesses and threats to the current approach.

In all regions there is now clear commitment to establishing NITAGs and all Regional Immunization Technical Advisory Groups have made strong statements with regard to the need to strengthen NITAGs. In addition, NITAG chairpersons have attended regional TAG meetings with immunization managers in all but one region to date and the fostering of exchanges between NITAGs have been received very positively by all and contribute to capacity strengthening. Country and intercountry NITAG workshops and meetings continue to be very successful and will further help accelerate progress. As shown in Table 4, key areas of support to NITAG were in capacity building. There will be a need to continue supporting improvement of committees' ability to review evidence and training members including on vaccinology.

Other positive developments include attention given to strengthening NITAGs at the Ministerial Conference on Immunization in Africa held on 24–25 February 2016 in Addis Ababa. During the last several years, there have also been examples of experience-sharing between well-developed NITAGs (e.g., United States, United Kingdom, Australia, Netherlands, and Lebanon) and NITAGs more early on in their development, and anecdotally this has been a beneficial activity. Country interest in

networking is evident in the establishment of a regional NITAG network in the South-East Asia Region and interest in the establishment of the GNN expressed at the international NITAG meeting in 11–12 May 2016; however, the SEAR network is fragile and the GNN is not yet formalized. With respect to the special approaches started to allow Member States with small populations to consider options such as subregional advisory groups referred to in last year's report, definite advances have been made in the Americas (for the Caribbean islands). In part this success is due to a long regional history of these small countries working together on different issues in education and in health. Other models are needed such as partnering with a NITAG in another country. How this is best done needs work given different constraints in different small countries in the different regions. As well as the effectiveness of these models for small countries as shown by adoption of recommendations and their relevance needs to be verified.

The management board of Gavi, the Vaccine Alliance has approved a framework for its 2016–2020 strategy that includes the importance of improving country leadership, and management and coordination, which includes NITAG strengthening. As a result, Gavi organized a consultation of stakeholders and major partners in August 2015 to engage them in this process in a manner that is sustainable and builds capacity at country level. Assisting countries to access Gavi funds allocated for health system strengthening or annually requested TCA to establish or strengthen NITAGs remains necessary. There has unfortunately not been much significant progress in allocating HSIS resources for longer term support of NITAGs, however the 16 country requests for NITAG support through TCA does illustrate increased acknowledgement of the important role that Gavi resources can play to establish and strengthen NITAGs.

More recently, we have seen competing interests and unclear roles for the way forward related to NITAGs in regards to 1) overlap with disease-specific vaccine introduction initiatives (e.g. PIVI and RAVIN) and avoiding conflict of interest, and 2) the presence of HTAs in many countries and its confusion with NITAG roles. As background, in 2014, the World Health Assembly urged Member States "to consider establishing national systems of health intervention and technology assessment in the systematic evaluation of properties, effects, and/or impacts of health technology" which includes medicines, vaccines and other health technologies. Member States were also urged "to identify gaps with regard to promoting and implementing evidence-based health policy." In some countries, confusion about the relative roles of the HTA and NITAG has arisen. The issues with disease-specific initiatives and HTA need to be assessed and resolved. With respect to single disease initiatives such as PIVI and RAVIN – these do not address breadth of vaccines needing NITAG assessment but may have expertise and evidence including VPD data that can feed into NITAG deliberations.

Although the Middle Income Country Strategy proposed by the MIC Task Force and endorsed by SAGE in April 2015 featured the strengthening of evidence-based decision-making as one of the four main areas of action identified as the pillars of this strategy, it was not funded and there has been only limited progress. The introduction of pneumococcal conjugate vaccine (PCV) into Malaysia, an upper-MIC, illustrates some of the issues that MICs face in using evidence-based decision making to support new vaccine introduction, especially in countries lacking strong surveillance data on burden of disease. For example, Malaysia does not have an independent NITAG but the Medical Development Division of the Ministry of Health Malaysia published an HTA Report on PCV

immunization (21); this report failed to make the case for PCV immunization because it lacked clear guidance and did not provide an evidence-based recommendation for PCV to be added to the NIP.

There is a notable lack of leadership from donors to support NITAG strengthening globally. This highlights the need for more emphasis on showing the benefit of NITAGs short and long term. The NITAG Assessment Tool (AMP-HPID, located at NRC) was developed at least partly for this purpose, specifically to better understand the factors contributing to NITAG performance, the complexities of integration versus independence of NITAGs, and how NITAG recommendations impact policy. Threats to future funding and staff turnover at AMP-HPID limited their ability to fully test the tool, and so there is currently very limited data on evaluating NITAG functionality. Despite these setbacks, there are ongoing and recently funded projects by partners to evaluate NITAGs. There is also an ongoing evaluation of SIVAC being conducted by the London School of Hygiene and Tropical Medicine (contracted by the BMGF) to better quantify the impact of the 10 year SIVAC initiative (results due in summer 2017).

The global community, while appreciating that NITAG establishment and functioning is an evolving process that needs to shape itself in the country context, still does not know the best way to improve the presence, quality and functionality of NITAGs in every country. This is especially true for outlier countries, whose infrastructure and context may not benefit from the criteria outlined in the current global NITAG guidance. These include small countries which do not have the technical resources to establish their own NITAG; for these countries, subregional NITAGs and/or partnerships with neighbouring country NITAGs may play a role. There are also high and middle income countries without functioning NITAGs, where we know there are systems in place that seem to be working but may not relate to the current model of NITAG functionality, in terms of independence or declaration of conflict of interest. We need to understand a way forward for these outliers and determine whether these countries can have assessments done that can let them meet criteria for having a functioning NITAG. For example, high income countries where NITAGs do not exist but evidence-based decision making is being done, assessments/evaluations to determine if NITAG criteria are being met and if not what changes are needed would be helpful.

Despite the model of SIVAC and its positive role in supporting countries in the initial processes of establishing NITAGs, it is evident that different approaches and types of support are needed as NITAGs mature. Taking into account the need to support NITAGs at all stages of development and the experience already available in many regions, one option would be a regional focus for future NITAG support involving: 1) designated NITAG focal persons in each WHO region and responsibility of NITAGs in advocating for NITAGs with Ministries of Health; 2) virtual subregional NITAG networks using such activities as quarterly webinars, hotline links to experts on specific technical issues, conducting NITAG assessments, and support from PIVI and RAVIN as technical resources; and 3) fora where 'leader' NITAGs share expertise and experience through mentoring developing NITAGs and work groups. To further implementation efforts and recognition of these expert groups, NITAGs need to be encouraged to expand their scope and focus also on monitoring implementation, evaluating impact, and recommending strategies to improve uptake of vaccination recommendations. Finally, to further the integration of NITAGs in the country policy process, there also needs to be networking and dialogue with policy decision-makers, sharing of policy briefs, and policy assessment. The GNN and NRC would form the bedrock of support for the regional activities

and foster collaboration and exchange of information among NITAG members globally. The subregional NITAG networks, with leadership from strong and interested NITAGs in each region, would be complementary to and support the GNN.

If a global agenda on NITAG strengthening is to move forward, the GNN and the NRC needs the support of the global community. The GNN secretariat has to have the technical capacity to do more than just organize meetings, the secretariat needs to continue developing resources, listening to countries, and providing the necessary help to countries for advocacy and other needs. Without the continued involvement of AMP-HPID as the GNN secretariat, how to support GNN and NRC going forward will need careful discussion.

Without an accelerated and joint effort, the GVAP objective of all countries having a functional NITAG by 2020 will not be achieved. Advocacy by involved stakeholders at national and global levels is necessary to ensure that sufficient time, effort and money are invested in both establishing and strengthening NITAGs. Currently, insufficient funding threatens the implementation of technical support activities by the collaborating centre (i.e., AMP-HPID), WHO and partners and limits the implementation of evaluations. Funding for the functioning of the secretariat of the global NITAG network and for maintaining the NRC is not yet secured. If a regional focus for future NITAG support is deemed essential, these activities and the regional focal points will need to be adequately funded. Countries still need to take an active role in establishing and maintaining NITAGs and to investigate innovative mechanisms to sustain funding for NITAGs.

8. Annexes: NITAG achievements: Country examples

Republic of Moldova NITAG

The Moldovan NITAG was established by ministerial decree in 2013 to provide independent advice on immunization policy and practice. The NITAG consists of 14 core members who represent wide diversity of medical disciplines. There are also 17 non-core members, including representatives of Ministry of Health, immunization programme, and medical societies. The Moldavian NITAG is generally believed to be a fully-functioning with a legal basis and terms of reference, links to the Ministry of Health, a core membership drawn from an appropriate range of disciplines and secretarial support provided through the National Centre of Public Health.

Since its establishment, Moldavian NITAG conducted four meetings and considered topics that were important for the national immunization programme and the Ministry of Health. The NITAG developed recommendations on removing BCG booster doses from national immunization schedule, introduction of one dose of IPV, switch from tOPV to bOPV, vaccination of risk groups against hepatitis A, seasonal influenza vaccination, and introduction of HPV vaccine. All NITAG recommendations were accepted and fully implemented by the Ministry of Health.

The Moldovan NITAG faces similar challenges as other NITAGs in middle-income countries, including difficulties in generating evidence-based recommendations because of limited capacity to conduct systematic literature review and lack of funding that leave the NITAG with very limited technical support from the Secretariat. In order to overcome these challenges the NITAG makes use of available information, such as WHO position papers, documents of Strategic Advisory Group of Experts together with detailed local data, to make evidence-based recommendations. WHO and international partners support in establishment and building capacity of Moldavian NITAG was essential. It included participation of NITAG members in regional meetings and trainings, visit to well-functioning French NITAG, and a formal NITAG evaluation.

The support from the international partners should be continued to ensure recognition of the important role played by NITAG and allocation of necessary resources, by the Ministry of Health. The international partners support will also be crucial for improvement of the quality of the NITAG recommendations by conducting trainings on evidence assessment methodologies and development of evidence-based recommendations.

Timor Leste NITAG

In June 2014 WHO/SEARO proposed Timor Leste to establish NITAG. Despite initial assumption that required expertise would not be available in Timor Leste, following discussions MCH Department of the MoH, decided to pursue with available experts. Draft ToR for the NITAG-Timor Leste and expertise required was developed in consultation with Immunization and Vaccine Development SEARO. In June 2014, WR, Timor Leste wrote to the Hon. Minister of Health describing importance of establishing NITAG with draft ToR and proposed types of experts to be considered. At that time the National Certification Committees for Polio Eradication had been established in Timor Leste and

was functioning smoothly with first Timorese pediatrician (out of the two in Timor Leste and working in private sector) as the chairperson. She was proposed as first NITAG chair.

For a period of more than one year WHO constantly advocated the importance of establishing NITAG, in official and unofficial forums. Based on the anecdotal information the main concerns of the MoH were; assumption that MoH Officials will lose the decision making authority over immunization programme and by appointing another independent group outside the MoH, it may become fault finding group of the MoH. Initially, MoH was not able to well comprehend the meaning of NITAG being an “independent group of experts”, how independent they are and how independently they can work. Above issues were discussed in several Council of Director’s Meetings (The main Policy Making Body of the MoH chaired by Hon. Minister of Health) in late 2014 and early 2015. Meanwhile, MoH had to take some key decisions on immunization on conducting wide age range Measles/Rubella/OPV catch-up immunization campaign, introduction of five new vaccines (Hepatitis B birth dose, IPV, MR 2 dose schedule, DPT/DT booster) to immunization programme, and TOPV to BOPV switch, as part of global and regional initiatives. The Hon. Minister of Health had to take these technical decisions with support of limited number of experts. To respond some adverse events after immunization and adverse comments came up during 2015 Measles /Rubella / OPV catch-up immunization campaign and other VPD control related programmes Hon. Minister needed the views of the national experts. This situation and intense advocacy by WHO led the MoH to consider formally establishing NITAG and through Ministerial Dispatch dated 10th November 2015, NITAG Timor Leste was formally established.

In November 2015, with WHO technical support orientation workshop on roles and responsibilities of NITAG and NITAG members was conducted. With the support of SIVAC consultant, INTERNAL PROCEDURES MANUAL OF NITAG TIMOR LESTE, NITAG work plan for 2016-2018 and 2016-2018 Budget were developed. In November 2016, GAVI Immunization Transition plan, allocated substantial amount of funds to proper functioning of NITAG for 2017 and 2018. In February 2017, MoH extended the ownership by appointing medical doctor as a secretary to the NITAG and provided space in MoH to establish NITAG secretariat.

Cote D’Ivoire NITAG

COMITE NATIONAL D’EXPERTS INDEPENDANTS POUR LA VACCINATION ET LES VACCINS DE LA COTE D’IVOIRE (CNEIV-CI)

The “CNEIV-CI” was established in December 2009 with support of AMP/SIVAC. The political will contributed to the creation of this structure and materialized by a ministerial decree of creation and appointment of NITAG members. The CNEIV-CI has a Descriptive Project that defines its terms of reference and Rules of Procedure that specifies its operation. Ordinary meeting takes place quarterly and extraordinary meeting when needed.

The NITAG in Ivory Cost includes 17 expert members, 9 Ex-officio members, 3 Liaison members and a technical and scientific secretariat. There is a policy for Management of Conflict of Interest through the following documents: Charter of public declaration of interests, Privacy Policy and public interest declaration form. There are 3 ways of requesting advice from the committee:

- Request from Ministry of Health (e.g., age limit for administration of rotavirus vaccine, free management of AEFI)
- Request from the EPI programme: e.g., introduction of meningitis vaccine (MenAfrivac)
- The committee itself (introduction of the HPV vaccine)

From January 2010 to March 2016, AMP/SIVAC provided the following support to the NITAG in Cote d'Ivoire:

- Material assistance to the secretariat
- Financial assistance for meetings organization
- Capacity building of NITAG's members: Workshop on Method of developing evidence based recommendation, 27-29 January 2015;
- Workshop on The use of economic data to support decision-making related to immunization, 29-30 March 2016

Role of the CNEIV-CI: to provide scientific and technical advice and recommendations to the Ministry of Health in the definition, implementation, monitoring and evaluation of immunization policies and strategies

Successes

Since its creation in 2009, the CNEIV-CI developed the following opinions and recommendations for the attention of the Minister of health:

- Recommendation for improvement of Expanded Program on Immunization (EPI) performances (2011)
- Recommendation for immunization against Human Papillomavirus (2016)
- Recommendation on the introduction of hepatitis B birth dose in the EPI (2016)
- Notice on age restriction of rotavirus vaccine in the EPI (2016)
- Recommendation on the introduction of MenAfrivac vaccine into the EPI (under development)

Also, a number of scientific papers were published:

- Establishment of a National Immunization Technical Advisory Group in Côte d'Ivoire: Process and lessons learned. Vaccine 30 (2012) 2588–2593
- Process for developing a recommendation : case of vaccination against hepatitis B at birth by the NITAG in Ivory Coast (Submitted to La Société Française de Santé Publique in January 2017)
- Immunization outside the Expanded Program on Immunization in Abidjan city, Cote d'Ivoire (Submitted to Austin journal of vaccine and immunotherapeutics in January 2017)

In 2014, an independent evaluation was conducted with the following objectives:

- Analyze how the committee works in relation to WHO standards and recommendations.
- Appreciate the effectiveness, efficiency and performance of the committee
- Identify gaps and needs of the committee for optimal functioning

Methodology used was desk review (TOR of Committee, Meeting reports and technical notes or recommendations issued, review of activities) and interviews with stakeholders (Committee Members, EPI Directorate, EPI Technical Partners, Representatives of research institutions). The evaluation did not use the newly developed 2016 HPID/SIVAC NITAG evaluation tool which will be used for this year's evaluation. The main recommendations from this evaluation were:

To the Ministry of Health:

- Strengthen communication with the committee
- Provide grants for the committee

To the Committee

- Elaborate TOR of committee bodies
- Search resources for workgroups
- Increase transport allowances for members
- Build capacity of members

Challenges

- Limited availability of some Members to attend meetings
- Insufficient funding (for NITAG meeting organization, working groups meetings, and conducting studies to have local data)

Mozambique NITAG

COMITE DE PERITOS DE IMUNIZAÇÃO (CoPI)

CoPI Mozambique was established in 2011 with support of AMP. CoPI is independent, multidisciplinary, representing a wide range of disciplines, covering aspects of the immunization area, development and vaccines regulations and epidemiology of diseases preventable by vaccines.

CoPI is composed by 15 members with head by Prof. Helder Martins (2011-2013) and by Prof. Jahit Sacarlal (2014- to date). It has a secretariat (MoH team) and there are around 25 observers and guests (universities, UNICEF, CDC, USAID, FNUAP, LOCAL NGOs, etc). All member and secretariat must fill Conflict of interest and confidentiality agreement before start working with CoPI. All official observers must filled the Confidentiality agreement.

General objective: To give opinions and technical advice that can guide the Health Authorities at the highest level and the programme managers in order to allow them to take policy and strategy of health, based in scientific evidence that results from an accurate analysis of the available information in terms of immunization and diseases preventable by vaccines, including selection of new vaccines, technologies and other prevention tools, the need of adjustments of the new immunization programmes and of the vaccination calendar.

Mode of operation: Dates meeting are set for 3 years. There are 2 ordinary meeting per year (April & November) and also extraordinary meetings. Convocations are sent one month before meeting

and re-convocation one week before again. During meeting, there are presentation of news about vaccines (SAGE meeting, Researchers, etc) and systematic review, and also drafting of minutes.

To issue recommendation, working groups are established or invite expert to present specific systematic review and Epi data, a member of CoPI or Head of EPI programme is invited to present information regarding the issue in discussion. A draft recommendation is prepared during meeting and final draft presented all on the last day. CoPI member review it within 1 week period. President finalize Recommendation (with background, recommendation and monitoring indicators) and then submission of approved recommendation to Ministry of Health who sometimes meet with him to explain it and finally dissemination including posting on NRC.

Monitoring recommendation is done during every meeting of the CoPI: member discuss with EPI manager on any challenges for implementation. If necessary the CoPI invite members to help to EPI programme. An annual report is developed and sent to MoH and CoPI members.

Until last April 2016, CoPI produced 28 recommendations available at <http://www.nitag-resource.org/>

Recommendations issued included some of the following topics:

2011

- Improvement of EPI performance: (how to reach those that have not been reached)
- Calculation of the EPI target groups
- Needs and Priorities for the introduction of new and underused vaccines
- Reliability of the EPI data and Epidemiological Surveillance of the diseases preventable by vaccines
- Sustainability of EPI financing
- EPI Logistics and cold chain
- Measles elimination
- New vaccine paradigms
- Human Resources (training, new staff)

Regarding introduction of new vaccines, CoPI has recommended the adoption of a very ambitious plan of introduction of new vaccines, which would allow reaching the Goal of the Millennium 4 until 2015.

- Vaccine against pneumococcus in 2012 – delay to 2013,
- Vaccine against Rotavirus in 2013, delay to 2015
- Vaccine against Human Papilloma Virus in 2014, pilot study;

2014

- Recommendation to introduce new vaccines for 2015 and 2016 (Rotavirus, IPV and Measles 2nd dose at 18 months)
- Recommendation to implementing monitoring system at private clinics/ hospitals and consultation rooms to collect number of children vaccinated

2016

- Recommendation in delay on application in the pilot study of Mosquirix vaccine

- Recommendation to change the PCV10 vaccine to PCV13 in Epi program

Strengths

- Good quality of the members
- Extremely competent members in their specific areas
- More specialists in country in case of replacement
- Importance of CoPI for MoH
- Increase conscience of EPI program

Challenges

- Activities not included into the national budget for EPI and thus, lack of financial after year 2 of support by AMP
- Lack of dedicated EPI staff in organize CoPI meeting,- only in last meeting I received first person
- Some members not present at meetings (not often)

9. References

1. Iroh Tam PY, Thielen BK, Obaro SK, Brearley AM, Kaizer AM, Chu H, et al. Childhood pneumococcal disease in Africa - A systematic review and meta-analysis of incidence, serotype distribution, and antimicrobial susceptibility. *Vaccine*. 2017;35(15):1817-27.
2. Matysiak-Klose D, Ahmed F, Duclos P, Falck-Ytter Y, Forland F, Houweling H, et al. Report on the 1st international workshop on procedures for the development of evidence-based vaccination recommendations, Berlin, Germany, 22-23 November 2010. *Vaccine*. 2012;30(14):2399-404.
3. Perronne C, Adjagba A, Duclos P, Floret D, Houweling H, Le Goaster C, et al. Implementing efficient and sustainable collaboration between National Immunization Technical Advisory Groups: Report on the 3rd International Technical Meeting, Paris, France, 8-9 December 2014. *Vaccine*. 2016;34(11):1325-30.
4. Toscano CM, Jauregui B, Janusz CB, Sinha A, Clark AD, Sanderson C, et al. Establishing a regional network of academic centers to support decision making for new vaccine introduction in Latin America and the Caribbean: the ProVac experience. *Vaccine*. 2013;31 Suppl 3:C12-8.
5. Adjagba A, Henaff L, Duclos P. The NITAG Resource Centre (NRC): One-stop shop towards a collaborative platform. *Vaccine*. 2015;33(36):4365-7.
6. Adjagba A, Senouci K, Biellik R, Batmunkh N, Faye PC, Durupt A, et al. Supporting countries in establishing and strengthening NITAGs: lessons learned from 5 years of the SIVAC initiative. *Vaccine*. 2015;33(5):588-95.
7. Blau J, Faye PC, Senouci K, Dagnan SN, Douba A, Saracino JT, et al. Establishment of a National Immunization Technical Advisory Group in Cote d'Ivoire: process and lessons learned. *Vaccine*. 2012;30(15):2588-93.
8. Burns JE, Mitrovich RC, Jauregui B, Matus CR, Andrus JK. Descriptive analysis of immunization policy decision making in the Americas. *Revista panamericana de salud publica = Pan American journal of public health*. 2009;26(5):398-404.
9. Duclos P. National Immunization Technical Advisory Groups (NITAGs): guidance for their establishment and strengthening. *Vaccine*. 2010;28 Suppl 1:A18-25.
10. Duclos P, Dumolard L, Abeysinghe N, Adjagba A, Janusz CB, Mihigo R, et al. Progress in the establishment and strengthening of national immunization technical advisory groups: analysis from the 2013 WHO/UNICEF joint reporting form, data for 2012. *Vaccine*. 2013;31(46):5314-20.
11. Duclos P, Ortynsky S, Abeysinghe N, Cakmak N, Janusz CB, Jauregui B, et al. Monitoring of progress in the establishment and strengthening of national immunization technical advisory groups. *Vaccine*. 2012;30(50):7147-52.
12. Gessner BD, Duclos P, Deroeck D, Nelson EA. Informing decision makers: experience and process of 15 National Immunization Technical Advisory Groups. *Vaccine*. 2010;28 Suppl 1:A1-5.
13. Koon AD, Rao KD, Tran NT, Ghaffar A. Embedding health policy and systems research into decision-making processes in low- and middle-income countries. *Health research policy and systems*. 2013;11:30.
14. Ngcobo NJ, Cameron NA. The decision making process on new vaccines introduction in South Africa. *Vaccine*. 2012;30 Suppl 3:C9-13.
15. Nijsten D, Houweling H, Durupt A, Adjagba A. Overlapping topics in advisory reports issued by five well-established European National Immunization Technical Advisory Groups from 2011 to 2014. *Vaccine*. 2016;34(50):6200-8.
16. Ricciardi GW, Toumi M, Weil-Olivier C, Ruitenberg EJ, Danko D, Duru G, et al. Comparison of NITAG policies and working processes in selected developed countries. *Vaccine*. 2015;33(1):3-11.
17. Saitoh A, Okabe N. Current issues with the immunization program in Japan: can we fill the "vaccine gap"? *Vaccine*. 2012;30(32):4752-6.
18. Senouci K, Blau J, Nyambat B, Coumba Faye P, Gautier L, Da Silva A, et al. The Supporting Independent Immunization and Vaccine Advisory Committees (SIVAC) initiative: a country-driven, multi-partner program to support evidence-based decision making. *Vaccine*. 2010;28 Suppl 1:A26-30.
19. Silva ML, Paget WJ, Mosnier A, Buthion V, Cohen JM, Perrier L, et al. Development of Seasonal Influenza Vaccination Recommendations: Relevance and Influence of the Evidence on the Decision-Making Process in France and the Netherlands. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2016;19(5):670-9.
20. Stecher D, Gaiano A, Biscayart C, Gentile A, Ayala SG, Lopez E, et al. National Immunization Commission: strengthening evidence-based decision making in Argentina. *Vaccine*. 2014;32(16):1778-80.
21. Takla A, Wichmann O, Carrillo-Santistevé P, Cotter S, Levy-Bruhl D, Paradowska-Stankiewicz I, et al. Characteristics and practices of National Immunisation Technical Advisory Groups in Europe and potential for collaboration, April 2014. *Euro surveillance : bulletin Européen sur les maladies transmissibles = European communicable disease bulletin*. 2015;20(9).
22. Tricarico S, McNeil HC, Head MG, Cleary DW, Clarke SC. Informing pneumococcal conjugate vaccine policy in middle-income countries: The case of Malaysia. *Vaccine*.

REVIEW

Role of the private sector in the provision of immunization services in low- and middle-income countries[†]

Ann Levin^{1*} and Miloud Kaddar²

¹Independent Consultant, Bethesda, MD, USA, ²Health Economist, World Health Organization, Geneva, Switzerland.
E-mail: kaddarm@who.int

*Corresponding author. Independent Consultant, 6414 Hollins Dr., Bethesda, MD, 20817, USA. Tel: +1-301-581 2422.
E-mail: annlevin@verizon.net

[†]The authors alone are responsible for the views expressed in this publication and they don't necessarily represent the decisions, positions, policy or views of the World Health Organization.

Accepted 19 April 2011

The authors conducted a literature review on the role of the private sector in low- and middle-income countries. The review indicated that relatively few studies have researched the role of the private sector in immunization service delivery in these countries. The studies suggest that the private sector is playing different roles and functions according to economic development levels, the governance structure and the general presence of the private sector in the health sector. In some countries, generally low-income countries, the private for-profit sector is contributing to immunization service delivery and helping to improve access to traditional EPI vaccines. In other countries, particularly middle-income countries, the private for-profit sector often acts to facilitate early adoption of new vaccines and technologies before introduction and generalization by the public sector.

The not-for-profit sector plays an important role in extending access to traditional EPI vaccines, particularly in low-income countries. Not-for-profit facilities are situated in rural as well as urban areas and are more likely to be coordinated with public services than the private for-profit sector. Although numerous studies on non-governmental organizations (NGOs) suggest that the extent of NGO provision of immunization services in low- and middle-income countries is substantial, the contribution of this sector is poorly documented, leading to a lack of recognition of its role at national and global levels.

Studies on quality of immunization service provision at private health facilities suggest that it is sometimes inadequate and needs to be monitored. Although some articles on public–private collaboration exist, little was found on the extent to which governments are effectively interacting with and regulating the private sector.

The review revealed many geographical and thematic gaps in the literature on the role and regulation of the private sector in the delivery of immunization services in low- and middle-income countries.

Keywords Immunization, private sector, health financing

KEY MESSAGES

- Relatively few studies have researched the role of the private sector in immunization service delivery in low- and middle-income countries; many geographical and thematic gaps exist in the literature.
- The literature review indicates that the private sector, in its different variants, is delivering a significant proportion of vaccinations in some countries.
- The private sector plays different roles in immunization delivery according to economic development levels, governance structure and the general presence of the private sector in the health sector.

Introduction

Immunization programmes provide many public health benefits to countries. At relatively low cost, these programmes contribute significantly to preventing communicable diseases. Governments consequently believe that it is their responsibility to support immunization programmes, both in terms of service delivery and funding. Almost all governments have legal regulations and health sector plans that endorse support of immunization programmes. In addition, many have policies stating that immunizations should be provided for free or for a nominal fee to all targeted populations, especially traditional Expanded Programme of Immunization (EPI) vaccines [diphtheria-pertussis-tetanus vaccine (DPT), BCG, polio-virus vaccine (OPV) and measles].

Although many governments would like to provide all preventive health services to their populations, not all are sufficiently well-equipped and financed to provide high quality services that are available and accessible to all. The private sector, which includes both private practitioners and not-for-profit organizations, often provides immunization services in its facilities and increases access to health services. However, it is unclear what percentage of total immunization services is offered through the private sector and how this share varies by country.

While many literature reviews have examined the role of the private sector in the provision of health services (Waters *et al.* 2003; Peters *et al.* 2004), none have focused specifically on immunization service provision. This paper’s objective is to fill the gap by summarizing existing literature on the private sector’s role in delivering immunization services in low- and

middle-income countries, and to identify potential lacunae and the need for additional research.

The theoretical starting point of the paper is that immunization services are both public and private goods. Immunization services are public goods since these provide positive societal externalities. Externalities of immunization programmes include herd immunity, control of contagious disease and the prevention of epidemics, which benefit society as a whole (Bloom *et al.* 2005). In addition, these services provide private benefits. Individuals place a value on the risk reductions obtained from vaccination differently (Berman 2004; Cook 2009), due to their assessment of risk of infection, history with the disease and level of risk-aversion. As a result of these differences in preferences, some people are willing to pay for immunization services at private health facilities rather than obtain them at public facilities. Furthermore, some groups will pay for vaccines not available in the public sector because of their perceived benefits.

It is assumed that the ability of a government to deliver and monitor immunization services provided in its country is affected by its economic level and its governance or stewardship capacity. Table 1 presents a typology of private sector health providers in low- to middle-income countries developed by the authors. Key terminology in the table are defined as follows:

- (1) Ad hoc: uncoordinated service provision that arises in response to local need;
- (2) Unregulated: services not subject to governmental regulations and/or standards of care;
- (3) Regulated: services subject to rules and regulations that are enforced by governmental or non-governmental entities; and

Table 1 Typology for role of the private sector in immunization service delivery by regulation, type of private sector and ‘fragile’ status

Type of private sector	‘Fragile’ countries	Low- to middle-income non-fragile countries
For-profit	<ul style="list-style-type: none"> • Ad hoc unregulated service delivery by private practitioners 	<ul style="list-style-type: none"> • Ad hoc unregulated service delivery by private practitioners • Unregulated provision of immunization services in private clinics/health centres, pharmacies w/private practitioners, and private maternity homes • Regulated private sector provision of immunization services and/or integration with monitoring and surveillance systems
Not-for-profit	<ul style="list-style-type: none"> • Unregulated provision of services by NGOs in clinics, health centres and hospitals • Contracting out of NGOs for immunization and other health services 	<ul style="list-style-type: none"> • Unregulated provision of services by NGOs in clinics, health centres and hospitals, sometimes using supplies from the public sector • NGO provision of and advocacy for immunization services with some level of regulatory policies/national guidelines • Provision of immunization supplies and equipment to NGOs • Public sector contracting out of NGOs for immunization and other health services to expand access

- (4) Contracting out: a contractual arrangement by which the government or other non-governmental entity provides compensation to private providers for a defined set of health services.

Low- to middle-income non-fragile countries often have limited resources to allocate to immunization services. In addition, their ability to monitor private sector provision of services (e.g. the quality of service delivery), or a government's stewardship over the private sector, is often limited due to insufficient financing and human resources. As a result, it is assumed that the private for-profit sector delivery of immunization services will range from ad hoc and/or unregulated to regulated. The relationship of the government with the not-for-profit sector differs since it is more likely to provide supplies to or contract out for its services.

Countries with limited governance capacity or 'fragile'¹ states are less able to provide and finance immunization service delivery. In these countries, gaps in service delivery are assumed to be filled by entities such as non-governmental organizations (NGOs) since these organizations enter 'fragile' countries to conduct emergency relief operations. In addition, some ad hoc delivery of health services takes place.

Often, governments view the private sector provision of immunization services as a 'gap filler' because of the responsibility of the government and externalities of immunization. However, given the need to work with the private sector to increase access to services, governments have specific strategies that they can employ to engage the private sector in service provision (Waters *et al.* 2003) in order to improve health outcomes: (1) regulation; (2) contracting; (3) financing and social marketing; (4) training; and (5) coordinating.

This paper reviews the literature on the role of the private sector in providing immunization services and the extent to which governments are employing strategies to oversee private sector delivery of immunization services. If the extent of the private sector's role in immunization service provision can be better documented, then it will be easier for the concerned governments to define appropriate incentives and regulations that will facilitate the two sectors' working together.

Methodology

The authors conducted a literature review using the following search terms: 'immunization', 'health services', 'private sector', 'non-governmental', 'for-profit' and 'developing countries'. Any paper that was published in 1990 or later was included in the search.²

First, the authors searched for published articles through PubMed. Secondly, they examined published findings from surveys, such as Demographic and Health Facility and WHO EPI coverage surveys, for findings on the share of services provided through the private sector. Thirdly, grey literature on the subject was also solicited through contacting various networks of people working in immunization service delivery, such as Technet.³

The authors conducted content analysis of the articles and other documentation found. The findings were categorized by

region, type of vaccines offered and whether services were for-profit. The following questions were focused on in the review:

- (1) How important is the private sector's role in immunization service delivery?
- (2) What functions does the private sector play and how does it affect the demand for and supply of immunization services?
- (3) What are the characteristics of users of immunization services in the private sector?
- (4) How is the government interacting with and regulating the private sector?
- (5) How well integrated is private sector service delivery into the national immunization and health systems?

Results

Articles considered for inclusion in the report were on the following topics: (1) private sector service delivery of immunization, (2) private sector delivery of health services, and (3) contracting of health services. Articles were included in the analysis if they discussed private sector delivery of immunization services specifically or referred to these services as part of a larger health service package. In total, 73 articles were vetted for the analysis and 37 articles were selected for inclusion (Table 2).

Share and importance of vaccinations provided through the private sector

Asia

Relatively more studies were undertaken to examine private for-profit and not-for-profit provision of immunization services in Asian countries than in other regions, perhaps because the private sector plays a larger role in provision of health services. The proportion of vaccinations provided by for-profit providers is available for five countries and ranges from 1–2% in Bangladesh to 17% in India (see Table 3). The proportion by

Table 2 Number of articles vetted and included in final analysis by type

	Private sector immunization services	Private sector health services	Contracting	Total
Articles vetted	22	43	9	73
Articles included in final analysis	22	8	7	37
Articles by region:				
Asia	12	3	1	16
Africa	4	1	1	6
Latin America	2	n.a.	1	3
Europe	1	n.a.	n.a.	1
North Africa/Middle East	1	n.a.	n.a.	1
No region	2	4	4	10

Table 3 Proportion of total immunization services delivered by the private sector in Asian countries

Country	% private for-profit immunizations	% private not-for-profit immunizations	Source
Bangladesh	1% (2005)	22% urban, 3% rural (2000); 4% (2005)	Bass 2006
	2% (1999) in Dhaka		Levin <i>et al.</i> 1999
		62% (NGOs in Dhaka)	Khan <i>et al.</i> 2004
Cambodia		30–40%	Bass 2006
India	10% in India		Peters <i>et al.</i> 2002
	17% children, 36% women using 1995–1996 National Sample Survey		Howard and Roy 2004
	26.9% urban, 15.4% rural Madhya Pradesh		Yoong 2007
	65.5% Hep B vaccines, 44.9% Hib; 100% typhoid/MMR/varicella in Chandigarh		Puri <i>et al.</i> 2007
Pakistan	3% of children, 4% of women		MOH Pakistan 2006 (EPI Coverage Evaluation Survey, 2006)
Sri Lanka	15% (33.5% Colombo, 0.7% Monaragala district; 0% in Anuradhapura, Trincomalee and Matale)		Agampodi and Amarasinghe 2007
Thailand	10% (33% in urban areas)		Madrid 1998c

for-profit providers is higher in urban than in rural areas, and in India and Sri Lanka in comparison to other countries.

Information on the share of immunization services provided by not-for-profit providers is only available for two Asian countries, Bangladesh and Cambodia (Bass 2006). In Bangladesh, NGOs' share is estimated to be 22% of immunization services in urban areas (city corporations and municipalities) and 3–4% in rural areas. The estimated share that they provide in rural areas ranges from 6% in the Khulna Division to 1% in the Dhaka and Barisal Divisions. In Cambodia, the share is estimated to be 30–40% of total services (Bass 2006).

In 'fragile' Asian countries such as Afghanistan, the majority of services are delivered through national and international NGOs (Ameli and Newbrander 2008), but the proportion provided by these agencies has not been documented. Private for-profit clinics or pharmacies provide services on an ad hoc basis (Pavignani and Colombo 2002), particularly in urban areas. Although governments are usually unable to monitor the provision of immunization services by the private sector in 'fragile' countries, various multilateral and bilateral organizations often contract with NGOs to deliver services. As part of these contracts, the managing organizations monitor the provision and/or quality of services provided by NGOs (MOHSW Liberia 2008). On the other hand, the private for-profit sector and NGOs without external funding are less likely to be regulated in 'fragile' states and services are often offered on an ad hoc basis (Pavignani and Colombo 2002).

Africa

In African countries, relatively few data are available on the role of the private sector in the provision of immunization services. The little information that is available suggests that for-profit providers play a relatively smaller role in the provision of immunization services than in Asian countries while not-for-profit providers have a more important role (see Table 4).

The studies report that the proportion of services given by for-profit providers ranges from 0.05% in Zimbabwe to 10% in Nouakchott, Mauritania, and is higher in urban and metropolitan areas than in rural areas.

Although anecdotal reports of NGOs' role in service delivery exist, accurate estimates of the proportion of immunization services provided by them are not available. Data on the proportion of total immunization services provided by NGOs are only available for two countries (Kenya and Ghana) from National EPI Reviews and EPI manager country estimates (Bass 2006). It is suggested but undocumented that NGOs are providing a significant share of traditional EPI immunization services under different arrangements in 'fragile states' such as the Democratic Republic of Congo, Sierra Leone, Burundi and Somalia.

Other studies in African countries focus on the type of services offered in for-profit and not-for-profit health facilities and have found that many of these are offering immunization services (Table 3). Data from facility surveys⁴ in five countries indicate that most (75% or more) not-for-profit health centres are offering immunization services, while the percentage of private for-profit facilities providing immunization varies widely, from 25% in Ghana to 81% in Kenya and Uganda.

Latin America

Only a few articles had information on the role of the for-profit health sector in immunization services in Latin America, as shown in Table 5. The services are generally provided by private paediatricians and other physicians in these countries. No studies were found on the proportion of immunization services provided by NGOs in Latin America. This finding could potentially be explained by the fact that vaccine laws exist in most Latin American countries promoting compulsory immunization services in the public sector (PAHO 2006).

Table 4 Proportion of total immunization services delivered by the private sector in African countries

Country	% private for-profit immunizations	% private not-for-profit immunizations	Type of vaccines offered	Source
Ghana		40% (mission hospitals)	Traditional EPI	Bass 2006 (National EPI estimates)
Ethiopia	0.7% (0–3.1% for individual regions)			Government of Ethiopia 2006 (2006 EPI-Cluster Sampling Survey)
Kenya		45–60% in some north and north-eastern districts (2000 estimate)	Traditional EPI	Bass 2006
Mauritania	10%		Traditional EPI, Hepatitis B, Hib	Ouedraogo 2003
Morocco	5%		Hepatitis B, Hib	Madrid 1998b
Zimbabwe	0.05–3%		Hib	Madrid 1998d

Table 5 Proportion of total immunization services delivered by the private sector in Latin American countries

Country	% private for-profit immunizations	% private not-for-profit immunizations	Source
Sao Paulo state, Brazil	1.3%	No information	de Soárez <i>et al.</i> 2008
Honduras	1.6%	No information	EPI Newsletter 1998
Nicaragua	5%	No information	EPI Newsletter 1998
Panama	15%	No information	EPI Newsletter 1998
El Salvador	5–10%	No information	EPI Newsletter 1998
Costa Rica	1–2%	No information	EPI Newsletter 1998

Europe

Very few studies are available on the role of the private sector in provision of immunization services in low- to middle-income European countries. In Turkey, one study in Umraniye Health District reported that 11% of immunization services are offered through the private for-profit sector (Topuzoglu *et al.* 2005).

In countries of the former Soviet Union, the formal private sector is limited due to high entry costs, underdeveloped voluntary health insurance and a lack of trust (Balabanova *et al.* 2008). Thus, not surprisingly, in a study in Uzbekistan, the authors concluded that NGOs are not offering immunization services in the country, although they often assist with social mobilization, vaccination training, and maintenance and repair of cold chain equipment (Bass 2006).

Functions played by the private sector

Increasing access to traditional EPI vaccines

Non-governmental health providers play an important role in filling gaps in public service delivery. A study on the role of not-for-profit organizations in immunization service delivery found that NGOs improve access to services by reaching populations in urban slums or remote or difficult regions, and in 'fragile' countries (Bass 2006). Other studies on contracting out of services to NGOs in low-income countries found that access to traditional health services, including immunization services, increased (Loevinsohn and Harding 2005; Ameli and Newbrander 2008; Liu *et al.* 2008).

A few studies have attempted to evaluate whether the private sector's role in immunization service delivery has affected

disparities in access, and have found that contracting out with NGOs can decrease disparities in accessibility to vaccination. Schwartz and Bushan (2004) investigated whether the provision of immunization services by NGOs in nine rural districts of Cambodia affected disparities in access. They found that more children were immunized in districts serviced by NGO contractors than in districts using the traditional government model where management of services remained with the government. Another study evaluated the effects of contracting out services on the equitable distribution of services in Bangladesh and Cambodia, and found a significant improvement in access to services for the targeted poor in both countries (Liu *et al.* 2004).

Various studies also indicate that the private for-profit sector increases access to traditional EPI vaccines for those who can afford to pay (Howard and Roy 2004; Topuzoglu *et al.* 2005; Agampodi and Amarasinghe 2007). For example, one study of private sector users in India found that 17% of respondents' children received their traditional EPI vaccinations at private facilities, while 36% of pregnant women received their vaccinations at private facilities (Howard and Roy 2004). Despite this increased access, the study indicates that users of private for-profit services are less likely to have received all traditional EPI vaccinations. The authors found that children and pregnant women immunized at private facilities due to proximity were slightly less likely to have obtained all of their traditional EPI vaccines than users of public services.

Introducing new vaccines

The for-profit private sector appears to play an active role in introducing new and underutilized vaccines in low- and

Table 6 Type of vaccines offered by the private for profit sector

	Traditional EPI vaccines	Non-traditional vaccines	Source
Asia			
Bangladesh		Non-EPI vaccines	Bass 2006
Cambodia	Tetanus	Hep B, rabies, typhoid, Japanese encephalitis (JE)	Soeung <i>et al.</i> 2008
India	Traditional EPI vaccines	Hep B, Hib, MMR, typhoid, varicella	Puri <i>et al.</i> 2007
Sri Lanka	Traditional EPI vaccines	JE, Hib, MMR, varicella, Hep A	Agampodi and Amarasinghe 2007
Thailand		HBV, Hib, varicella	Madrid 1998c
Africa			
Mauritania		Hep B, Hib	Ouedraogo 2003
Morocco		Hep B, Hib	Madrid 1998b
Europe			
Turkey		MMR, Hib, varicella	Topuzoglu <i>et al.</i> 2005

middle-income countries, as can be seen in Table 6. This role is particularly important in non-GAVI-eligible middle-income countries that cannot get newer vaccines at low or subsidized prices. At times, though, the for-profit private sector is driven by pharmaceutical marketing campaigns to introduce new and costly vaccines, such as rotavirus, pneumococcal, inactivated polio virus and human papillomavirus virus. These campaigns tend to use aggressive marketing and have direct links with prescribers and key opinion leaders.

A survey of Asian policy makers (DeRoeck 2004) indicated that they believed private sector service delivery of vaccines to be important for several reasons: (1) to create public demand for a vaccine before it is introduced into the public sector; (2) to provide a vaccine before the public sector is ready to do so; and (3) to provide vaccines to clients of higher income while the public sector provides vaccines at no cost to low-income clients. The for-profit private sector can target small selected populations that are willing to pay for newer vaccines. In addition, the private for-profit sector may collaborate with the public sector to introduce new vaccines (DeRoeck 2004).

Madrid (1998a,b,c,d) conducted case studies in three countries—Thailand, Morocco and Zimbabwe—on the role of the private sector in the introduction of new vaccines. She found that the role differed for each of the countries. In Thailand, the private market was not a direct driver of new vaccine integration in the public sector but did influence the choice of product and the local manufacturing arrangements (Madrid 1998c). In Morocco, the study concluded that the private sector did influence the public sector's introduction of new vaccines, although it was one of several factors that affected the decision-making (Madrid 1998b). In Zimbabwe, the study concluded that the private sector had no influence on the introduction of Hepatitis B vaccine in the public sector, but was likely to be more influential in the introduction of Hib vaccine since its burden of disease was not known (Madrid 1998d).

Users of private sector services

Consumers of the private for-profit sector are motivated to use their immunization services for different reasons: (1) the

services are more convenient due to closer proximity or better hours of operations; (2) the services are the only ones available; and (3) the perception that services have advantages over other alternatives, such as higher quality (Table 7). In a survey in India, for example, 47% of private sector users preferred to utilize these immunization services due to their closer proximity, while 53% were motivated by perceived higher quality (Howard and Roy 2004). In another survey in Mauritania (Ouedraogo 2003), a third of the immunization users accessed the private sector for reasons of convenience (e.g. shorter wait, service continuity and convenient hours), while two-thirds were motivated by perceived higher quality of care and competence of personnel. In Sri Lanka, reasons for using private sector services were availability of non-EPI vaccines, combined vaccines and efficiency of services (Agampodi and Amarasinghe 2007).

Clients that use private for-profit facilities to obtain immunization services were more likely to have higher educational levels and higher family income than public sector users in Sri Lanka (Agampodi and Amarasinghe 2007), and higher socio-economic status based on asset ownership and occupation than non-users in Turkey (Topuzoglu *et al.* 2005). The clientele of private for-profit services are also more likely to be located in urban than in rural areas. On the other hand, the study by Howard and Roy (2004) also revealed that a small percentage of private for-profit service users in India are of low-income. Surveys of consumers with lower socio-economic status indicated that they preferred to use these health facilities because of proximity, access and/or shorter waiting time.

Consumers of services by non-profit organizations, on the other hand, are more likely to be of lower income than users of for-profit clinics (Schwartz and Bushan 2004). They are likely to use these immunization services because of their greater access, lower cost and/or higher perceived quality.

Regulation of the private sector and impact on system quality

The few studies that examined the quality of immunization services provided by the private for-profit sector concluded that

Table 7 Characteristics of users of private for-profit services

Country	Characteristics of users	Reasons for using private sector	Source
Mauritania		67%: quality of reception, quality of care, competence of personnel; 33%: shorter wait, service continuity and convenient hours	Ouedraogo 2003
India	Chandigarh: uptake of newer vaccines greater with higher mother's education and father's education	Child sample: 35% for proximity, 39% for quality; Pregnant women: 33% for proximity, 38% for quality Availability of vaccines throughout the week and easy access	Puri <i>et al.</i> 2007 Howard and Roy 2004 (NSS study sample from 1995–1996) Government of India 1993 (1988 EPI coverage survey)
Sri Lanka	Users more likely to be of lower birth order, Tamil, Buddhist or Hindu, and have higher monthly family income		Agampodi and Amarasinghe 2007
Turkey	Users more likely to be of higher socio-economic status, age, being born in Istanbul and less likely to be in a peripheral health centre		Topuzoglu <i>et al.</i> 2005

it is sometimes inadequate. In a study in Cambodia, Soeung *et al.* (2008) found that health workers in private facilities lacked knowledge on immunization schedules, waste and vaccine management practices, and did not exchange health information with the public sector. In Mauritania, a study of private sector practices found that health professionals lacked knowledge on immunization provision and did not have the correct cold chain equipment (Ouedraogo 2003). Aljunid and Zwi (1997) in Malaysia found that private providers did not always store their vaccines at the correct temperature. Other research articles on the private sector provision of health services in general also emphasize similar problems with quality of care (Bustreo *et al.* 2003; Waters *et al.* 2003).

Despite problems associated with quality in private sector service provision, the literature on government regulation of private sector health service delivery suggests that it is usually insufficient. Some low-income countries have legal frameworks for regulation but inadequate enforcement, while others have neither (Lagomarsino *et al.* 2009). No articles were found specifically on the effectiveness of the regulation of private for-profit sector provision of immunization services, although studies in Cambodia and Mauritania (discussed above) stated that the governments planned to introduce regulation of immunization services to improve their quality.

Regulation of NGO provision of immunization services to ensure that national guidelines on quality of care are followed is more common, particularly when the government or development partners have contracts with NGOs to deliver services. In Afghanistan, for example, contracts with NGOs specify the quantity and quality of immunization services to be delivered and also focus on inputs or outputs such as immunization rates (Palmer *et al.* 2006). Liu *et al.*'s review of contracting out projects found, however, that these projects are more likely to improve quality of care if it is well defined and indicators are well developed (Liu *et al.* 2008).

Table 8 Government support for private sector vaccination services

Country	MoH provision of vaccines and supplies to private for-profit sector	MoH provision of vaccines and supplies to not-for-profit sector	Source
Sub-Saharan Africa			
Cameroon	Yes	Yes	Waters <i>et al.</i> 2004
Ghana		Yes	Levin <i>et al.</i> 2001
Mauritania	Yes		Ouedraogo 2003
Asia			
Cambodia	Yes	Yes	Schwartz and Bushan 2004; MOH/NIP Cambodia 2006

Integration of private health facilities into national immunization and surveillance programmes

A few studies report on examples of the integration of the public sector's immunization programme with the private sector. In these countries, the public sector is collaborating with private sector institutions so that immunization service delivery and surveillance can be extended to parts of the country without access to services. Often the government provides vaccines, equipment and other supplies to private facilities (see Table 8). As a result, the programme managers can ensure that these adhere to national standards. In addition, it can obtain data on the number of immunizations that are given in private sector health facilities and/or pharmacies. In Cameroon, for example, each health area has a lead health facility, which can either be public or private, and it coordinates the distribution of vaccines and supplies and reports coverage rates of the area (Waters *et al.* 2004).

In Uganda, the government also entered into a public–private partnership with not-for-profit providers. It provides vaccines, equipment and operational grants to these providers. Currently, 29 private not-for-profit facilities (13.5%) in 214 sub-districts are overseeing referrals and management of other health facilities in their sub-district (Balabanova *et al.* 2008). Other examples of integration occur through contracting and are found in Cambodia (Schwartz and Bushan 2004), Rwanda (Soeters *et al.* 2006) and Afghanistan (Ameli and Newbrander 2008).

Discussion of findings and gaps in the literature

Despite the fact that immunization is a public good, has positive externalities and governments have an interest in being the main provider of vaccination, the literature review indicates that the private sector, in its different variants, is active and delivering a significant proportion of vaccinations in some countries.

In low-income countries, private for-profit and NGO health facilities are providing immunization services and helping to improve access to traditional EPI vaccines, particularly in Asian countries. In addition, these facilities are providing services to higher-income clients who are willing to pay for better perceived quality, shorter waiting times and closer proximity. The literature review suggests that NGOs often play a larger role in immunization service delivery than do private for-profit providers in low-income countries, since their facilities are situated in rural as well as urban areas. Further, NGO services are more likely to be coordinated with public services, either through formal contracts or through more loosely-structured mechanisms in low-income countries.

In ‘fragile’ countries, the review suggests that NGOs are playing a particularly important role in delivering immunization services, often under contracting-out arrangements with governments and their partners. Other gaps in provision of vaccination are filled through ad hoc service delivery by for-profit providers and non-profit providers.

In middle-income countries, the private for-profit sector is active and plays a number of roles. It often acts to facilitate early adoption of new vaccines and technologies before introduction and generalization by the public sector. In addition, the review suggests that private practitioners increase access to services by offering traditional EPI vaccines. The extent that governments are regulating these providers is not known.

Many of the strategies for engaging the private sector are being used in low-income countries, including ‘fragile states’, i.e. contracting, training, financing and coordinating; and paradoxically immunization services may be more well regulated in these countries than in middle-income countries. Contracting and financing strategies have been shown to be effective at bringing services to the poor and at least partially ensuring that quality services are provided. However, little is known about the extent to which service provision is effectively regulated when formal contracting arrangements are not in place.

In middle-income countries, the literature suggests that the private for-profit sector’s role in provision of immunization services is more prominent than in low-income countries.

The extent to which these services are regulated and what type of regulation is most effective has not been documented. Given the concerns about the quality of immunization service delivery in private health facilities, more research is needed on regulation of private sector immunization services in middle-income countries.

Potential mechanisms that can be introduced to engage the private sector include: (1) involving the sector in policy and programme setting—for example, private providers can be represented on national immunization technical advisory groups (NITAG) as well as other policy-making organizations; (2) introducing financial and other types of incentives to increase immunization coverage and/or access to services; and (3) regulation of service quality, payment mechanisms and fees.

There are many geographical and thematic gaps in the literature on the role and regulation of the private sector in the delivery of immunization services in low- and middle-income countries. Limited studies exist on: (1) the adequacy of quality of care of immunization service delivery in the private for-profit sector; (2) the impact of private for-profit service delivery on disparities in services delivery; (3) the effectiveness of regulating the private for-profit sector; and (4) the impact of private sector immunization service delivery on demand for traditional EPI, new and underutilized vaccines.

Conflict of interest

None declared.

Endnotes

- ¹ Fragile states have been defined by the UK Department for International Development (DFID) as states that are unwilling and/or incapable of delivering basic services to their populations. These countries have a lack of effective political processes to influence the state to meet social expectations, and weak institutions and governance systems (Alliance for Health Policy and Systems Research, WHO 2008).
- ² Some previous research on the role of the private sector in the 1980s is found in Frelick (1986).
- ³ The Technical Network for Strengthening Immunization Services (Technet) serves as a forum where issues relevant to the delivery of immunization services are discussed.
- ⁴ DHS Service Provision Assessment (SPA): Ghana SPA 2002, Kenya SPA facility inventory 1999, Rwanda SPA 2001, Tanzania SPA 2006, Uganda SPA 2006 (MEASURE Demographic and Health Surveys, online at: <http://www.measuredhs.com/aboutsurveys/spa/start.cfm>).

References

- Agampodi SB, Amarasinghe DA. 2007. Private sector contribution to childhood immunization: Sri Lankan experience. *Indian Journal of Medical Science* **61**: 192–200.
- Aljunid S, Zwi A. 1997. Public and private practitioners in a rural district of Malaysia: complements or substitutes?. In: Bennett S, McPake B, Mills A (eds). *Private Health Providers in Developing Countries: Serving the Public Interest*. London: Zed Books, pp. 40–53.
- Ameli O, Newbrander W. 2008. Contracting for health services: effects of utilization and quality on the costs of the Basic Package of Health Services in Afghanistan. *Bulletin of the World Health Organization* **86**: 920–28.

- Alliance for Health Policy and Systems Research, WHO. 2008. Neglected health systems research: health policy and systems research in conflict-affected fragile states. Research Issue 1. Online at: http://www.who.int/alliance-hpsr/AllianceHPSR_ResearchIssue_FragileStates.pdf.
- Balabanova D, Oliveira-Cruz V, Hanson K. 2008. *Health sector governance and implications for the private sector*. Technical Partner Paper 9. Washington, DC: Results for Development Institute and the Rockefeller Foundation.
- Bass A. 2006. A review to identify the role of civil society organizations in immunization. Unpublished paper prepared for the GAVI Secretariat and GAVI CS Task Team.
- Bloom DE, Canning D, Weston M. 2005. The value of vaccination. *World Economics* 6: 15–39.
- Bustreo F, Harding A, Axelsson H. 2003. Can developing countries achieve adequate improvements in child health outcomes without engaging the private sector? *Bulletin of the World Health Organization* 81: 886–95.
- de Soárez PC, Valentim J, Sartori AM, Novaes HM. 2008. Cost-effectiveness analysis of routine rotavirus vaccination in Brazil. *Revista Panamericana de Salud Publica* 23: 221–30.
- DeRoock D. 2004. The importance of engaging policy-makers at the outset to guide research on and introduction of vaccines. *Journal of Health, Population and Nutrition* 22: 322–30.
- Frelick G. 1986. *Immunization and the developing world: the role of the private sector*. Washington, DC: National Council for International Health. Based on a conference in La Jolla, California, 1985.
- EPI Newsletter. 1998. *Immunization and private sector participation*. EPI Newsletter 20 (5), Expanded Program on Immunization in the Americas. Washington, DC: Special Program for Vaccines and Immunization, PAHO.
- Government of Ethiopia. 2006. *EPI Cluster Sampling Survey, DTP3 coverage in Ethiopia*. Addis Ababa: Government of Ethiopia, Family Health Department.
- Government of India. 1998. *EPI coverage survey*. New Delhi: Government of India.
- Howard D, Roy K. 2004. Private care and public health: do vaccination and prenatal care rates differ between users of private vs. public sector care in India? *Health Services Research* 49: 2013–26.
- Khan MM, Khan SH, Walker D *et al.* 2004. Cost of delivering child immunization services in urban Bangladesh: a study based on facility-level surveys. *Journal of Health, Population and Nutrition* 22: 404–12.
- Lagomarsino G, Nachuk S, Singh Kundra S. 2009. *Public Stewardship of Private Providers in Mixed Health Systems: Synthesis report from the Rockefeller Foundation-sponsored initiative on the role of the private sector in health systems*. Washington, DC: Results for Development Institute.
- Levin A, Howlader S, Ram S, Siddiqui SM, Razul I. 1999. *Case study on the costs and financing of immunization services in Bangladesh*. Bethesda, MD: Abt Associates, Partnerships for Health Reform. Special Initiatives Report No. 21.
- Levin A, England S, Jorissen J, Garshong B, Teprey J. 2001. *Case study on the Costs and Financing of Immunization Services in Ghana*. Bethesda, MD: The Partners for Health Reformplus Project, Abt Associates, Inc.
- Liu *et al.* 2004.
- Liu X, Hotchkiss DR, Bose S. 2008. The effectiveness of contracting-out primary health care services in developing countries: a review of the evidence. *Health Policy and Planning* 23: 1–13.
- Loevinsohn B, Harding A. 2005. Buying results? Contracting for health service delivery in developing countries. *The Lancet* 366: 676–81.
- Madrid Y. 1998a. The introduction and use of new vaccines in the public and private sectors. Unpublished paper. Global Programme on Vaccines and Immunization, Vaccine Supply and Quality Unit, World Health Organization.
- Madrid Y. 1998b. The introduction and use of new vaccines in the public and private sectors. Country report: Morocco. Geneva: World Health Organization.
- Madrid Y. 1998c. The introduction and use of new vaccines in the public and private sectors. Country report: Thailand. Geneva: World Health Organization.
- Madrid Y. 1998d. The introduction and use of new vaccines in the public and private sectors. Country report: Zimbabwe. Geneva: World Health Organization.
- MOH Pakistan. 2006. Pakistan EPI Coverage Evaluation Survey 2006, Third Party Evaluation – National Summary Report. Islamabad: Ministry of Health.
- MOH/NIP Cambodia. 2006. Guidelines for private sector immunization. Phnom Penh: National Immunization Program, Ministry of Health.
- MOHSW Liberia. 2008. Situational assessment of Liberia's capacity for performance-based contracting of non-governmental organizations for the delivery of the delivery of the Basic Package of Health Services. Monrovia: Ministry of Health and Social Welfare.
- Ouedraogo A. 2003. Etude sur l'apport des structures sanitaires privées a la vaccination de routine. Rapport de mission. Ministry of Health/European Union, Islamic Republic of Mauritania.
- Palmer N, Strong L, Wali A, Sondorp E. 2006. Contracting out health services in fragile states. *British Medical Journal* 332: 718–21.
- Pavignani E, Colombo S. 2002. Afghanistan Health Sector Profile. World Health Organization. Draft. Online at: http://www.aims.org.af/services/sectoral/health/health_sector_profile_aug_02.pdf, accessed 10 March 2006.
- Peters D, Yazbeck A, Sharma R *et al.* 2002. *Better Health Systems for India's Poor: Findings, Analysis, and Options*. Washington, DC: World Bank.
- Peters DH, Mirchandani GG, Hansen PM. 2004. Strategies for engaging the private sector in sexual and reproductive health: how effective are they? *Health Policy and Planning* 19(Suppl. 1):i5–21.
- Puri S, Bhatia V, Singh A, Swami HM, Kaur A. 2007. Uptake of newer vaccines in Chandigarh. *Indian Journal of Pediatrics* 74: 47–50.
- Schwartz B, Bushan I. 2004. Improving immunization equity through a public-private partnership in Cambodia. *Bulletin of the World Health Organization* 82: 661–7.
- Soeters R, Habineza C, Peerenboom PB. 2006. Performance-based financing and changing the district health system: experience from Rwanda. *Bulletin of the World Health Organization* 84: 884–9.
- Soeung SC, Grundy J, Morn C, Samnang C. 2008. Evaluation of immunization knowledge, practices, and service-delivery in the private sector in Cambodia. *Health Policy and Nutrition* 26: 95–104.
- Topuzoglu A, Ozaydin G, Cali S *et al.* 2005. Assessment of sociodemographic factors and socio-economic status affecting the coverage of compulsory and private immunization services in Istanbul, Turkey. *Public Health* 119: 862–9.
- Waters H, Dougherty L, Tegang S *et al.* 2004. Coverage and costs of childhood immunizations in Cameroon. *Bulletin of the World Health Organization* 82: 668–75.
- Waters H, Hatt L, Peters D. 2003. Working with the private sector for child health. *Health Policy and Planning* 18: 127–37.
- Yoong J. 2007. Does decentralization hurt childhood immunization?. Unpublished paper, Department of Economics, Stanford, CA, USA.

Title: A Review of the Private Sector's Contribution to Immunization Service Delivery in Low, Middle, and High-Income Countries

Corresponding author's contact info:

Rachel Mitrovich, MPH
Boston University School of Public Health
715 Albany Street
Talbot Building, Room 221
Boston, MA 02118
rmitrovi@bu.edu
+1 707 332-2088

Author's affiliations & qualifications:

Rachel Mitrovich, MPH
Boston University School of Public Health

Melanie Marti, MD
Department of Immunization, Vaccines and Biologicals
World Health Organization

Margaret Watkins, MPH, BSN
Global Immunization Division
Centres for Disease Control & Prevention

Philippe Duclos, DVM, PhD
Department of Immunization, Vaccines and Biologicals
World Health Organization

Key words: Immunizations, private sector engagement, public health services, delivery of healthcare, vaccine coverage, monitoring and regulations

Abbreviated running title: Private Sector's Contribution to Immunization Service Delivery

Key messages:

- Evidence remains limited about the private sector's contribution to immunization service delivery, impact on equity of immunization services, and interaction between pharmaceutical industry and the private sector.
- While there are a number of countries that have successfully engaged with the private sector, others have had limited involvement or experienced challenges with private sector provision of immunization services.
- Given countries' varying and unique characteristics, a standard approach to engaging the private sector is unrealistic. However, identifying characteristics of strong programmes to guide and adapt to the country context is useful.

Conflicts of Interest: The authors have no competing financial interests.

Acknowledgements (including all sources of funding)

A special thank you to those who were interviewed to identify country specific information on the private sectors role in immunization service delivery and their review of the document to ensure information was captured correctly: Dr José Ignacio Santos, National Autonomous University of Mexico; Dr Jaleela S. Jawad, Ministry of Health, Bahrain; Dr Marian AlHajiri, Public Health Director, Bahrain; Dr Monique Landry, Ministère de la Santé et des Services sociaux du Québec; Dr Alissar Rady, World Health Organization, Lebanon; Dr Ole Wichmann, Robert Koch Institut, Berlin. Additionally, we would like to express our gratitude to Dr Lyndon Lee Suy, Republic of Philippines Department of Health, for providing information about private sector engagement in the Philippines. Further, a special thank you to Ananda Amarasinghe, World Health Organization, Regional Office for the Western Pacific who reviewed the document and provided insight on the topic.

DRAFT

Abstract

Success of the Global Vaccine Action Plan and improvements in vaccination coverage rates at the sub-national, national, and global levels requires optimizing the private sector's engagement in the area of immunization delivery. However, the impact of the private sector on vaccination coverage and practices varies between countries and remains poorly understood. Expanding on a previous review published in 2011, the authors conducted a literature review and semi-structured interviews to assess private providers engagement in immunization delivery across low, middle, and high-income countries. To identify potential contributions, challenges, and ways to optimize the private sector's engagement in the area of immunization delivery, three key dimensions of the private sector were assessed: (1) contribution to immunization services; (2) impact on equity of immunization services; (3) interaction between pharmaceutical industry and private sector. Based on limited sources of information we were able to identify that while there are a number of countries that have successfully engaged with the private sector and used it as a platform to improve their immunization programmes, others have minimal involvement or have experienced challenges. To productively engage the private sector for immunization service delivery there needs to be an increased collaboration between private sector providers and National Immunization Programs. This should start with a review of the private sector contribution to immunization delivery as well as programme monitoring and adverse events and disease surveillance, and a look into the quality of service delivery and an effort to identify and inventory key stakeholders in private sector involved or potentially involved in vaccination. This could be followed by determination of optimal model of public private engagement, expansion of dialogue to achieve common immunization goals, and development of collaborative activities and potentially memorandum of understanding, agreements or contracts. Globally too few efforts have assessed the current and potential contribution of private providers to national immunization programmes.

I. Introduction

With the ability to prevent communicable disease at the population level, vaccinations are a core component of the human right to health (1). In 2012, the World Health Assembly adopted the Global Vaccine Action Plan (GVAP) with the aim to provide equitable access to vaccines by 2020 (1). Acknowledging a global health landscape that supports collaboration between sectors, the GVAP sets auspicious goals that are only attainable through shared responsibility and partnerships (1). Specifically, the success of GVAP and further improvements in vaccination coverage rates at the sub-national, national, and global levels requires optimization of interaction between public and private health care sectors. However, the impact of the private sector on vaccination coverage and practices varies between countries and remains poorly understood. This not only applies to contribution of vaccinations delivered, but interaction between sectors, level of monitoring, and degree of regulations imposed on private providers.

In every country the national immunization program (NIP) leads immunization service delivery with varied contributions from the private sector. Traditionally, immunizations are part of a package of basic health services provided and financed by the government and often supplemented by international donors in low and middle-income settings. A country's ability to deliver these services is directly affected by its economic level, governance, and administrative capacity (2). Frequently, in developing countries, the desire to provide preventative services is challenged by finances, health infrastructure, and competing health priorities (2). The private non-for-profit sector (NGOs) often provides immunization services to fill these gaps and increase access to services whereas the private for-profit sector more typically provides services to those with the ability to pay.

Globally, there are a variety of models that describe the role of public and private providers and the health sector in delivery of immunization services. In the majority of low and middle-income countries (LMICs), publicly funded immunization services are provided solely by public providers, but in many countries private providers also contribute to the delivery of these services (2,3). Private providers may work full-time in the private sector or they may be based out of the public sector and serve as part time private providers delivering immunizations; these private providers may also operate in school and occupational health services (4). High-income countries often rely on private providers as their primary means for delivering immunizations due to financing of vaccination services through established health insurance schemes. Increasingly, middle and low income countries are using the private sector to deliver core health care services funded by Universal Health Coverage programs (2,3).

In 2011, Levin and Kaddar reviewed the role of the private sector in the provision of immunization services in LMICs and found that private providers play different roles in immunization delivery according to a country's economic development, infrastructure to support public healthcare services, and presence of private entities in the health sector (2). However, there were significant geographical and thematic gaps in their findings due to the general lack of published literature on the topic. Our paper seeks to expand on the previous review by examining evidence published since their analysis, and also considering evidence from high-income countries and key informant interviews. Specifically, we consider three dimensions of private sector engagement: (1) contribution to immunization service delivery; (2) impact on equity of immunization services; (3) interaction between pharmaceutical industry and private sector. Following description of these dimensions, we identify potential contributions and challenges, as well as ways to optimize the private sector's engagement in the area of immunization delivery.

II. Methods

A literature review was conducted between May and August 2016, to assess the provision of vaccination services provided by entities outside of the government, including private independent practitioners¹, private for-profit providers, and private not-for-profit non-governmental organizations (NGOs). The review was limited to the private sector's role in service delivery and did not consider the role of the private sector through philanthropic donations or pharmaceutical company support.

Primary literature was identified in bibliographic databases: PubMed, Scopus, Cochrane Library, and Web of Science. The search was also extended to the WHO library database WHOLIS, which provides access to research published at the local level not indexed in MEDLINE or similar tools. Additionally, the literature review included World Bank reports on private sector healthcare utilization at the country level identified in the World Bank Documents and Reports repository. Indexed and free-text search terms were used in a variety of combinations and included 'immunization', OR 'immunization programs', OR 'vaccination', AND 'private-sector', OR 'public-private sector partnerships', OR 'health services', OR 'non-governmental', OR 'for-profit', OR 'regulation'. Articles were included if they were set in low and middle-income countries published after 2009 (therefore not included in the Levin and Kaddar analysis), or set in high-income countries without a date restriction. Following the literature review, an additional search was conducted to identify any articles that cited Levin and Kaddar, as well as additional references found in articles identified in the literature review.

After screening of titles, abstracts were reviewed for inclusion if they directly addressed private sector delivery of immunization services, monitoring and regulation of immunization services (including mention in overall analysis of pharmaceutical regulations), or if immunization services were referenced as a package of maternal and child health services. Abstracts were excluded if they addressed private sector funding mechanisms or vaccine financing, immunization delivery in the context of a public health emergency (e.g. H1N1), or if they did not directly address private sector delivery of services.

Articles from selected abstracts then underwent a full review and were included in the report if they reported on one or more of the following topics: (1) immunization services provided by the private sector; (2) health care services provided by the private sector; (3) health facility assessments conducted in the private sector; (4) private provider attitudes and knowledge about immunizations; (5) contracted health services; (6) regulation of health services; (7) immunization coordination mechanisms; (8) immunization coverage (9) equity of health services; (10) immunization decision-making processes including National Technical Advisory Groups; (11) interaction between pharmaceutical industry and private sector relative to immunization.

To expand information on the topic, semi-structured interviews were conducted with countries where geographic gaps in the literature were identified to obtain a more comprehensive assessment spanning all WHO regions. A limited convenience sample of countries was selected in which personal and direct contact with key informants could facilitate quick interaction and successful discussion. These countries either had known issues in engaging with the private sector or employed a successful model that could provide additional information. Identified countries included Mexico

¹ Private providers may include physicians, nurses, midwives, and pharmacists who are directly involved in the administration of vaccines; they may work full time in the private sector, full time in the public sector, or part-time in the private sector.

and Canada for the Region of the Americas, Germany for the European Region, and Lebanon and Bahrain for the Eastern Mediterranean Region. Countries in the African and South-East Asia Regions were not included because of existing information in these regions. Additionally, preliminary results from a survey on private sector utilization recently conducted in the WHO's Western Pacific Region were incorporated into this review.

Immunization experts (Table I) were identified by the WHO Secretariat and select members of the Strategic Advisory Group of Experts (SAGE) on Immunization. They either served as national immunization managers or WHO country office representatives serving as focal points for immunization in their country. Experts were contacted via email regarding their participation. Interviews were conducted over the phone and lasted roughly one hour. Interviews included six open-ended questions that addressed (1) role of private sector in immunization delivery including percentage of immunization services delivered; (2) interaction and relationship between public and private sectors; (3) quality standards including post market surveillance and reporting of doses; (4) equity of immunization service delivery. After each interview, a summary was shared with the interviewee to ensure accurate representation.

III. Results

The search identified a total of 1,166 references, of which 417 were duplicates. In total, 246 articles were reviewed for analysis, 31 publications were selected for inclusion, and 5 semi-structured interviews were conducted (Figure I, Table II). Data captured during the literature review and interviews were organized according to the following categories for ease of reporting:

1. Contribution to Immunization Service Delivery
 - a. Vaccine Share (results presented by WHO region²)
 - b. Training & Quality Standards
 - c. Advocacy for Immunization
 - d. Programme Monitoring and Post Market Surveillance
 - e. Decision-Making
2. Impact on Equity of Immunization Services
3. Interaction Between Pharmaceutical Industry and Private Sector

1. Immunization Service Delivery

A. Contribution to vaccine delivery

Levin and Kaddar's review found limited information on the contribution of private providers to vaccine delivery, and there has been limited additional information since their review. The contribution to vaccine delivery can be assessed as the *proportion of private facilities providing vaccination services* or the *proportion of vaccinations provided by private providers* ("vaccination share").

Proportion of private facilities providing vaccination services

In Kenya 34% of for profit private facilities and 80% of NGO-managed facilities provided vaccinations (Sood and Wagner 2013) (Table III). In the Republic of Korea, 60% of private providers offered vaccinations (Cho et al, 2010). In a study in four cities in Cambodia (Soeung et al 2008), the percentage of private providers who provided some form of immunization services was 65%, but the

² <http://www.who.int/about/regions/en/>

percentage varied by antigen. Hepatitis B vaccine was provided at 56% of sites, tetanus vaccine at 35% of sites, but other vaccines were rarely provided.

Proportion of vaccinations provided by private providers (“vaccination share”).

WHO African Region

Oluoha et al’s retrospective study in Nigeria considered the utilization of private health facilities for immunization delivery. In 2009, the Ministry of Health (MOH) established a Memorandum of Understanding (MOU) with private health facilities in four local government authorities (LGAs) in Abia state for the provision of free immunization services. The collaboration included support from the MOH and in return private health facilities had to comply with the MOH’s reporting, monitoring, and evaluation requirements. In the four LGAs that fully operationalized the public-private partnership (PPP)³, 45% of private health facilities offered immunizations. These facilities provided 21% of overall immunization services compared to 79% administered by the public sector⁴ (6). In 2010, one year after the PPP was instated, the mean third dose diphtheria-tetanus-pertussis (DTP3) vaccination coverage was 95% in the four PPP local governments compared to 59% in those who did not operationalize the PPP; the national reported DTP3 coverage in Nigeria was 68% at this time (6). Oluoha et al. postulated that the discrepancy in DTP3 coverage rates between local governments who instated the PPP and those who did not could be attributed to increased accessibility to health facilities in the PPP areas (6).

Kenya’s utilization of the private for-profit sector in immunization delivery was assessed by Sood and Wagner. Based on the 2010 Kenya Service Provision Assessment (SPA), 34% of for-profit facilities sampled provided immunizations compared to 80% of NGOs, and 88% of public sector facilities (3). Of note, further analyses that also incorporated Demographic and Health Surveys (DHS) showed that the odds of a child receiving no immunizations was 4.8 times higher in areas where all health facilities were for-profit compared to areas with no for-profit facilities. (3). In a different study, only 29% of private for-profit facilities reported receipt of technical or financial assistance for immunizations (8).

A survey in Kampala, Uganda, found that 30% of respondents received services from private facilities, 68% from public facilities, and 2% obtained vaccines from outreach services provided by public providers and NGOs (7). Reasons reported for low involvement of the private sector included lack of financial support for immunization activities from the government and diminished technical capacity (7).

According to a World Bank report, in Ghana the government provides free vaccines and promotional materials to private facilities without a contractual agreement; however, vaccine delivery share was not quantified (Makinen et al. 2011).

In Libreville, Gabon, Ategbo et al. found that coverage rates for routine antigens in the for-profit sector were greater than those in the public sector. Coverage of the third doses of diphtheria, pertussis, tetanus, vaccine and oral and inactivated polio vaccine DPT/OPV-IPV (90.2%) and measles (82.5%) vaccine was higher at private clinics compared to 74.5% and 64.4% respectively at public clinics (5). Explanation for the difference between the two sectors was not provided. Looking at Sub-Saharan Africa as a whole, Wagner et al. assessed the performance of public and private sector (for-

³ These local governments were located in urban/semi-urban areas and consisted of multiple private health facilities.

⁴ Public sector facilities were large teaching hospitals who had large catchment area and provided outreach activities to neighbouring communities where they immunized children in their homes (6).

profit and NGO) delivery of BCG vaccination where the private sector provides approximately half of all healthcare services (8). BCG coverage within the same calendar month of birth at private facilities was 9.2 percentage points lower than in public health facilities (45.3% versus 54.5%) (8).

WHO South-East Asia Region

In the WHO's South-East Asia Region, information on the share of immunization services provided by the private sector was only available in studies from India and Bangladesh. In Bangladesh, non-government organizations (NGOs) supplement government provided health services due to rapid growth in the country's population. In Dhaka city, NGOs deliver more than 95% of immunizations through a PPP (Uddin et al. 2012,). The national Expanded Programme on Immunization (EPI) supports this partnership by ensuring vaccine supply and logistical support⁵ to both the municipal government and NGOs (11). Municipal governments in turn assist NGOs in planning, monitoring, and evaluation of immunization programs (11).

In urban Gujarat State in India, private providers contribute a large share of immunization services (24%), similar to other urban areas in India (UNICEF Coverage evaluation survey, 2009). In less urbanized, lower per-capita income states, the private sector contribution is lower. In a separate study that used private sector vaccine sales data, Sharma et al. found that in the 2009-2012 birth cohort in 16 states, the private sector contributed towards overall (both urban and rural) vaccination coverage: 4.7% towards BCG, 3.5% towards measles, 2.3% towards DPT3, and 7.6% towards OPV3 (Sharma et al. 2016). In a different study (Sharma et al, 2015) the private sector contribution to Hib vaccine coverage was 4% and varied among Indian states (0.3% - 4.6%) (12).

WHO Western Pacific Region

Within the WHO's Western Pacific Region, four articles referenced for-profit vaccine share. Proportions of total immunization services delivered by the for-profit sector ranged from 10% in the Philippines to 60% in the Republic of Korea (13,14). In Cambodia, the percentage of private providers who provided immunization services was 65%. The estimated private sector contribution to vaccination coverage in the Philippines was reported to be 10% (interview) (14). (Table III).

In the Philippines, Patel et al. assessed coverage rates for a birth dose of hepatitis B (HepB-BD) across private and government hospitals, and government clinics. In private hospitals median timely HepB-BD, coverage was 50% and median total coverage (all hepatitis B vaccines received in the series) was 80%, compared to 87% and 80% respectively at government hospitals (15). At government clinics, median timely HepB-BD coverage was 90% and median total coverage was 100% (15).

A similar study conducted in Viet Nam assessed coverage of Hep-BD within 72 hours of birth (16). The proportion of birth doses delivered within 72 hours was lowest (47%) in the province with the highest percentage of deliveries in private facilities (16). This was attributed to weak linkages between private health facilities and the national EPI with EPI services are restricted to EPI facilities (16). Rigorous evidence was not provided to support this conclusion and statistical testing was not reported.

The private sector in Cambodia provides services to two-thirds of their population (17). Soeung et al. quantified immunization practices among private practitioners in four major cities; 65% of the private providers/health clinics surveyed provided some form of immunization services but

⁵ Disposable syringes and needles, refrigerators, cold boxes, vaccine carriers, and vaccine transportation cost.

the proportion varied by antigen (17). Hepatitis B vaccine and tetanus toxoid were most commonly provided (55.9% and 35.4% respectively)⁶ (17). Other routine vaccines such as BCG (9.4%), DTP (3.9%), and measles (3.9%) were rarely provided, whereas provision of newer vaccines such as rabies (26.0%), typhoid (11.8%), and Japanese encephalitis (10.2%) were more common (17).

WHO Eastern Mediterranean Region

Since the 2011 review by Levin and Kaddar, two articles included private sector immunization share for Pakistan (Table 3). To enhance information, interviews were conducted for Bahrain and Lebanon.

According to official estimates in Pakistan, the government provides approximately 97% of immunization services to children through the EPI (18). However, a recent population survey in Karachi (an urban area) revealed that 25% of immunized children had received vaccinations from the private sector (18). The discrepancy may possibly be due to a concentration of private providers in urban areas. The main source of private sector immunization were private for profit physicians (80%), with a smaller proportion provided by the non-profit sector (amount not quantified) (18). A separate study conducted by Zaidi et al. compared newborn BCG immunization and use of tetanus toxoid during pregnancy in contracted NGO facilities with government facilities in two remote rural districts in Pakistan (Chital and Thatta). BCG immunization coverage was 10.6 percentage points higher in contracted NGO clinics than in government clinics ($p < 0.01$) in Chital, but not in Thatta district. No difference was seen in tetanus toxoid coverage between contracted NGO facilities and government facilities in either district (19).

While the public sector administers more than 90% of vaccines for free in Bahrain, the for-profit sector fills the gap ($< 10\%$) via a collaborative relationship (20). Vaccines administered at certified private health facilities are procured through the MOH, but the private provider sets the fee. In Lebanon, the MOH reports that roughly 60% of the population receives vaccines in private for-profit clinics (21). These vaccines are administered by general practitioners, paediatricians, and gynaecologists in their private practices. The remaining 40% of vaccines are administered by a large network of government supported health centres and managed by NGO, for a nominal fee (21).

WHO Region of the Americas

Articles (2) pertaining to the role of the private sector in the Region of Americas were limited to the United States and the Caribbean. To supplement published data, 2 interviews were conducted for the province of Quebec, Canada and Mexico. Estimates of the share of immunizations given in the private sector ranged from 5% in Mexico to 61% in the United States (Table III) (22,23).

In Mexico, an estimated 95% of childhood and adolescent vaccines are reported to be administered in the public sector with no fee (23). Accounting for roughly 5% of immunizations, the private sector is primarily used for vaccines that are not included in the EPI schedule and providers determine the price for vaccines procured outside of the government (e.g. Hepatitis A and varicella). For influenza vaccine, an estimated 8-9% of doses are administered by private practitioners (23). In the Caribbean, vaccination of children is predominantly administered by the public sector through a network of clinics (24). The private sector administers vaccines to an estimated 10%-20% of each birth cohort (24).

⁶ The authors reported that this is most likely due to the private sectors integrated approach to maternal and neonatal healthcare.

Vaccine administration in the United States is mixed between private providers and public health clinics with the private sector being dominant. This is largely due to the Vaccines for Children (VFC) program, a federally funded PPP, which provides vaccines at no cost to children who meet certain eligibility requirements⁷. Vaccines are distributed at no charge to private physicians' offices and public health clinics registered as VFC providers; approximately 70% of VFC providers are private providers (25). To capture the role of the private sector, Groom et al. utilized the National Immunization Survey (NIS) between 1996 and 2004 to determine proportion of respondents whose children exclusively visited private providers. Of immunizations administered to young children, 61% were administered exclusively in the private sector (22). The remaining 29% were split between the public sector (16%) and those administered in a combination of one or two provider types (23%) (22,26).

In Canada, immunization programs fall under provincial and territorial jurisdiction. They determine schedule and delivery systems based on recommendations put forth by the National Advisory Committee on Immunization. Historically, in Quebec, the private sector has administered a higher proportion of vaccines to children under five years of age than the public sector. However, over the last 10 years, the situation has gradually reversed with roughly 80% of vaccine administered by the public sector and 20% by the private sector (27). This change happened for a number of reasons, notably the increasing complexity of the immunization schedule, strict application of vaccine storage standards, and time dedicated to answering questions of hesitant parents or individuals (27). Delayed vaccination was reported to be more common in the private sector compared to the public sector (28). Vaccines included in the immunization schedule are provided to the private sector by the MOH free of charge; vaccines provided outside of the schedule are procured by independent providers and charged at a price dictated by the private provider (27).

WHO European Region

For the WHO European Region, information was drawn for three articles and one interview. One article was a comprehensive coverage assessment conducted by the Vaccine European New Integrated Collaboration Effort's (VENICE II) that assessed vaccine administration by provider type across 29 European Union and European Economic Area countries. Of the 14 countries that provided immunizations to children under three years of age, private sector share ranged from 0.5% in Hungary to 100% in Luxemburg and Ireland (Table III) (29).

In Catalonia, Spain, Borrás et al. , found that 68.7% of children received vaccinations in public health centres compared to 31.3% in private offices (30). The private sector accounted for a larger proportion of non-EPI vaccines; 63.5% of children receiving varicella vaccine and 47.4% receiving pneumococcal vaccine, compared to 36.5% and 52.6% respectively at public health centres (30). A study in Greece found that 33.4% of parents sampled had their child vaccinated by their private paediatrician where they paid a doctors fee, 65.7% by providers with fees covered by insurance, and 0.9% by a public health clinic (31). A separate survey of immunization program managers reported a 70% share of vaccinations in the private sector in Greece.

In France, the majority of vaccines are reported to be administered in the private sector. Ninety-percent of immunizations (child <3yrs) are administered by private primary (29). In these settings the client purchases vaccine from a pharmacist and brings it to their physician for administration. The remaining 10% of infant immunizations are administered in public maternal and

⁷ Under the age of 19, Medicaid eligible, American Indian or Alaskan native, uninsured, or underinsured.

child health clinics that provide services to children six years of age and under (29). For vaccines procured through the private sector, the Social Security Scheme reimburses 65% of the cost of vaccines with the remaining financial responsibility falling on the individual or their voluntary complementary insurance (Vaccine European New Integrated Collaboration Effort 2006).

Similar to France, approximately 90% of vaccines administered in Germany are estimated (from interview) to occur in the private sector (33). The remaining 10% are administered by occupational health professionals or public health offices (33). There is no central government financing for immunizations, rather statutory and private health insurance policies pay for all recommended vaccines making them free of charge to the public. Payment for vaccines administered outside of the recommended schedule is out-of-pocket or supported by voluntary policies of single insurance companies.

B. Quality Standards

Information used to describe quality assurance mechanisms was drawn from 8 articles and two interviews. Of the studies assessed in LMICs, a systematic review noted that quality standards for immunization delivery in the private sector were inferior to their public sector counterparts (4). In most high-income countries, mechanisms to monitor the quality of immunization delivery in both public and private health sectors were in place (26).

In Nigeria, where a MOU established requirements for both government and private providers, gaps were identified in immunization service quality. Highlighted gaps included the need for additional mechanisms to ensure proper vaccine storage and up-to-date knowledge (6). A study in Kampala, Uganda found that unqualified people participating in the immunization program were predominantly found in private facilities and that this was a main reason why consumers preferred public facilities (7). Supervisory visits in the Philippines showed that private sector staff did not store vaccine appropriately and were unaware of the significance of the vaccine vial monitor (15). These examples are consistent with previous studies conducted in the private sector in Malaysia that documented similar problems with vaccine maintenance, staff knowledge, and quality of care (2,17).

For vaccines included in the immunization schedule in Quebec, Canada, private physicians are required to complete a public health contract at the regional and provincial level. The contract outlines guidelines and quality standards for vaccine administration, including that private physicians undergo a storage and handling audit prior to approval. Following approval, further auditing, surveillance, and monitoring is conducted at the regional level. By December 31, 2018, for regulation purposes, all vaccines administered in both the private and public sector will be required to be entered in a Provincial vaccine registry (27).

The MOH in Bahrain sets quality standards for clinics requesting permission to provide vaccination services. Quarterly and annual evaluation visits are conducted by the MOH using a standard checklist are conducted to ensure fulfilment of required standards for provision of vaccinations services. . Quarterly visits are conducted to ensure proper cold chain and storage procedures, whereas the annual monitoring visit is a comprehensive instructive field visit that includes adverse events following immunization (AEFI) reporting, capacity building, equipment, knowledge, compliance with standard operating procedures, and data quality. An annual data quality and accuracy assessment is also conducted using the WHO Data Quality Service (DQS) tool.

The United States conducts extensive monitoring of vaccination services through the VFC program where it provides oversight of approximately 90 million VFC doses distributed annually (Whitney et al. 2014). When a provider enrolls in the program, they must adhere to oversight

requirements that include a one-time initial site visit to educate provider staff, periodic site visits, development of a vaccine accountability system and a fraud and abuse policy. During site visits in 2010, government grantees identified vaccine management deficiencies and developed corrective action plans for 57% of private providers and 46% of public providers (25). Providers may be suspended or terminated if they do not meet requirements after implementing corrective action plans.

C. Advocacy for Immunization

Information regarding the private sector's role in advocating for immunization was gathered only during interviews with Germany, Mexico, and Quebec, Canada. In Germany, information on the benefits and risks of vaccination is disseminated to the public by a large number of stakeholders including national and state health authorities, professional societies, insurance companies, and vaccine manufacturers. It has been noted that these messages are often divergent due to competing interests, making advocacy amongst private providers challenging (33). This varies from the situation in Quebec where the private provider's role is to advocate and educate the public on the importance of vaccination. In Mexico, manufacturers use the private sector to lobby for the introduction of new vaccines.

D. Program Monitoring and Post Market Surveillance

Since Levin and Kaddar's review, six publications were identified that discussed reporting of vaccine coverage rates, adverse events following immunization (AEFI), and notifiable diseases. This information was supplemented with information from four of the interviews.

In India, the government provides limited monitoring and supervision at the field level for private practitioners (35). Assessment teams who conducted visits to private practitioners providing hepatitis B vaccines noted that reporting of doses administered from the private sector were fragmented and sporadic. In states where there were coordinated mechanisms for the private sector to systematically collect information on vaccination status of children, results were consistently reported (35). In a separate study conducted in Gujarat State, only 22% of private providers stated that they reported doses administered to the government; 69% did not report and 9% reported that government staff collected their data in lieu of self-reporting (36). For notifiable disease surveillance, only 54% of private providers reported that they would report a suspected case of measles and 63% would report acute flaccid paralysis (36). Of the providers who reported treating a patient with an AEFI, only 15% reported the case (36).

Patel et al.'s assessment in the Philippines found that only 36% of private hospitals reported vaccination coverage to the government immunization program, compared to 96% of government clinics (15). Approximately half of private hospitals reported that they had not received a supervisory visit within the previous six months compared to 6% at government clinics and 31% at government hospitals (15). The MOH does not have jurisdiction in the private sector for reporting AEFI, but encourages them to report AEFI in a timely manner to the manufacturer or the Food and Drug Administration (14). Considering the Western Pacific Region as a whole, the availability of a system/institution(s) to monitor and regulate immunization services by private providers was greatest in high-income and lower-middle income countries, with the greatest gaps seen in upper-middle income countries (37).

In Mexico, where the private sector plays a minimal role in immunization delivery, the government does not implement program monitoring mechanisms or post market surveillance for

the private sector. Private providers are encouraged, but not obligated to report AEFIs and there are no clear penalties for failure to report (23). Guidelines for reporting and vaccine administration are made readily available to the private sector. In Germany, where the private sector is utilized for immunization activities, the National Public Health Institute (NPHI) does not have regulatory control over vaccine distribution, administration, or cold chain in the private sector. The NPHI receives claims data from the Associations of Statutory Health Insurance Physicians only on a voluntary basis to assess coverage and conduct independent post-marketing assessments of vaccine-effectiveness and impact (33). By law, AEFI and regulatory issues are to be reported by private physicians or vaccine manufacturers to the National Regulatory Authority.

Vaccine use in the United States of America is monitored by a biologics surveillance system and various immunization surveys (26). The Centers for Disease Control and Prevention's (CDC) biologic surveillance system collects voluntary reports from manufacturers on the number of doses they distribute (26). Private facilities receiving vaccine from the VFC program are required to report vaccine administration rates and AEFI as a term of their contract (22,26). In Bahrain, the MOH issues circulars requesting that all health facilities offering immunizations, including private providers, report administrative data and AEFI (20). Similarly, in Quebec, the government mandates that any private provider offering immunizations report both administrative data and AEFI to the MOH within a designated timeframe (27).

E. Decision-Making

Because the literature review yielded only two articles (from United States and Republic of Korea) pertaining to the private sector's contribution to decision-making, information on the private sector's role in decision-making primarily came from the key informant interviews. Involvement in decision-making varied significantly across countries, regardless of private sector vaccine share.

In Bahrain, where there is a comprehensive and supportive partnership between the public and private sectors, the private sector is included in the decision-making process. A nominee from the private sector serves as a core member of the National Immunization Technical Advisory Group (NITAG), contributing to technical and scientific issues and final recommendations. Additionally, the private sector is notified in advance when modifications are made to immunization policies, vaccination schedules, and administration procedures to ensure buy-in and cooperation. Similar to Bahrain, the Korean Advisory Committee on Immunization Practices (KACIP), an advisory body of the MOH, provides practical guidance and policies for immunization. The Committee includes representatives from private associations, experts, and government officials, but private providers do not play a role in decision-making (13). When the MOH approves a new recommendation they work with both public and private sectors to plan implementation of the recommendation (13).

In Germany, the NITAG is hosted by the NPHI and is responsible for developing vaccine policy. NITAG recommendations are the basis for the "vaccine directive" that is endorsed by the Federal Joint Committee (G-BA). A permanent guest from the G-BA sits on the NITAG, as well as several voting members who are private physicians serving as individual experts. Private physicians have voting rights whereas the permanent guest does not (33). Physician associations may officially ask the NITAG to develop a specific recommendation, but the NITAG decides what topics are to be prioritized and recommended. After the NITAG develops a draft recommendation it is sent to federal states, the G-BA, and relevant societies for comment. It is at the discretion of the NITAG to consider comments received from outside private parties in formulation of the final recommendation. Decisions outside of the NITAG purview (decisions on distribution, administration, reimbursement,

and tender contracts) are the responsibility of private sector partners including insurance companies, physicians, physician associations, vaccines manufacturers, and wholesalers (33).

While Mexico sees minimal engagement of the private sector for immunization delivery, the country maintains private sector representation for decision-making on the National Immunization Council. The council includes representation from different government agencies, the Mexican Academy of Paediatrics, internal medicine groups, and private providers. Only one to two seats are held by the private sector placing them in a minority vote (23). Quebec, Canada utilizes a similar process where the private sector representative sits on the provincial expert committee that provides recommendations to the MOH. Nominees from the private sector serve as official consultants, and when the MOH implements a new program or major changes, it is based on a scientific consensus between private physicians and public health experts.

In the United States, the Advisory Committee on Immunization Practices (ACIP) is a group of medical and public health experts that develop recommendations on use of vaccines in the civilian population of the United States. (26). The ACIP includes 15 voting members, 14 of which have expertise in a vaccination related field; 1 member is a consumer representative who provides perspectives on the social and community aspects of vaccination (38). In addition to the 15 voting members, ACIP includes 8 ex officio members who represent other federal agencies that share responsibility for immunization programs in the United States, and 30 non-voting representatives of liaison organizations that bring related immunization expertise (38).

2. Impact on Equity of Immunization Services

Since Levin and Kaddar's review, eight studies have evaluated the impact of the private sector on equity of immunization services with additional information gathered in three interviews..

Two studies conducted in LMICs, found that for-profit sector services favour those in urban locations and/or those with higher family incomes (Wagner et al. 2014; Basu et al. 2012). The private sector's contribution to vaccination coverage in India was limited to states with high per capita GDP and high levels of urbanization (10,12). Similarly, in the urban area of Kampala, Uganda, the odds of using private facilities for immunization services were three times higher in the wealthiest household income quintile than in the lowest wealth quintile. (7). In Kenya, Sood and Wagner found that in geographic areas with a larger proportion of for-profit providers, the population was wealthier, more educated, and had fewer children per household than areas with a larger proportion of non-profit private providers(3). For-profit providers were more common in urban compared to rural areas; smaller urban-rural differences were seen in the NGO sector (8).

Since the VFC program was enacted in the US, immunizations have become more equitable across the public/private sector divide, yet disparities remain (22). Typically, children are less likely to be up-to-date with their immunizations if they live below the poverty line, reside in urban areas, and are non-White (22). Groom et al. found that children receiving immunization services in the private sector were predominantly white (60%), from suburban areas (52%), and at or above the poverty line (71%), compared to those receiving immunization services in the public sector (38%, 32%, and 41% respectively (22).. This suggests that the most at-risk children, both racially and economically, are served by the public sector.

Although lack of published evidence exists in Bahrain and Germany, equitable access to immunization services is reported in key informant interviews to be minimal. In Bahrain, HPV is offered in the private, but not in the public sector as it is currently under review for burden of disease, cost effectiveness, and feasibility of vaccination. If the MOH decides to incorporate the

vaccine into the standard schedule after the review period, access to the vaccine would be more equitable between the two sectors. Similarly, in Germany, equity is not an issue if the vaccine is included in the recommended schedule. If it is not included (e.g., meningococcal B vaccine) then it is at the discretion of the insurance company and favours those of a higher socio-economic status if paid out-of-pocket.

3. Interaction between Pharmaceutical Industry and Private Sector

One topic that was not included in Levin and Kaddar's review and was intended to be the third dimension for this paper was the private sector's interaction with the pharmaceutical industry. During the literature review no information was identified that pertained to regulatory requirements and standard operating practices for vaccines procured by the private sector. Specifically, we were unable to identify if private providers were securing only licensed vaccines and how they engaged in business with the pharmaceutical industry, including regulations imposed on procurement mechanisms for donated vaccines. Thus, information was limited to what was collected during interviews with key informant interviews from Germany and Bahrain.

In Germany, once a vaccine is licensed and brought to market by the manufacturer, it is purchased by large, private wholesalers who distribute vaccines to private physicians and local pharmacies. Quality standards are implemented and enforced by the manufacturer on the basis of defined regulatory requirements laid forth in national and European guidelines such as the European Medicines Agency (EMA) or the European Directorate for the Quality of Medicines & HealthCare (EDQM). Furthermore, within the European Union (EU) Official Control Authority Batch Release (OCABR) network every vaccine batch is tested for quality compliance with EDQM requirements before marketing in the EU. Vaccine batches already delivered into the supply chain in Germany are subject to control by respective state authorities (33). To ensure reliability and safety of vaccines in Bahrain, the MOH procures all vaccines, receives all shipments, and checks them upon arrival before distribution to private providers, thus guaranteeing that all vaccines are procured from licensed manufactures and meet the same standards as vaccines administered in the public sector (20).

V. Discussion

The contribution of the private sector to immunization service delivery and its level of engagement with the government varies widely between countries and is not fully understood. Our review attempted to fill in the thematic gaps identified by Levin and Kaddar and to identify characteristics of a strong programme to guide and adapt to the country context. In LMIC's, we found that access, affordability, and quality of immunization services were influenced by the scope of the government's involvement. Contractual agreements, communication channels, performance monitoring, and regulation of the private sector are more likely to improve quality of vaccination services. By adding the dimension of high-income countries we were able to identify governments that had successfully engaged with the private sector and used them as a platform to extend their immunization programmes. This highlights that a concerted effort between sectors to ensure vaccine access, coupled with policies that cross cut both sectors, should in theory result in higher coverage rates.

This review suggests that for-profit services may be more difficult to assess than not-for-profit because delivery of vaccination services is not as closely monitored and reporting to the government is sporadic at best. Ensuring equitable access to immunization services is instrumental to achieve coverage goals. For-profit services favour those in urban areas and of higher socio-

economic status, creating potential for inequity if the poorest populations are unable to access public sector services and those services are sub-optimal. Studies in this review suggest that service delivery in private-for-profit sector was associated with poor performance due to lack of training, quality standards, and programme monitoring, corroborating Levin and Kaddar's findings (2).

Contracting services to NGOs has also been shown to improve access to immunizations and primary health care services (2,6). Not-for-profit private services were more likely to be coordinated with government services through formal contracts or MOUs than for-profit services (Levin & Kaddar 2011, Oluoha et al. 2014; Mackintosh et al. 2016). Not-for-profit services are more commonly provided in rural areas or poor populations, where access to health services is limited. This suggests that contracts or MOUs that encompass technical support, with defined program goals and consistent monitoring, have a greater chance of producing quality vaccination service delivery and ultimately higher immunization coverage.

One of the more concerning findings of this review is the lack of program monitoring and adverse event reporting and participation in vaccine preventable disease surveillance in the private sector. In LMICs with monitoring and surveillance programmes in place, evidence suggests that it is often insufficient with gaps in enforcement and adherence. Even in high-income countries where there is adequate government infrastructure and mechanisms to capture this information, reporting is often suboptimal. Inadequate reporting from the private sector results in loss of information on coverage, vaccine-preventable disease incidence, and adverse events, which can affect planning, prioritization, resource allocation, and timely response to outbreaks and vaccine safety concerns. Additionally, our understanding of how private providers engage in with the pharmaceutical industries is minimal at best. Lack of knowledge in this area makes it difficult to formulate recommendations for optimal vaccine introduction and use and regulatory requirements.

Although this review describes private sector engagement for immunization across a wider spectrum than a previous review, our ability to fully describe the situation is limited by available data. Since Levin and Kaddar in 2011, the scope and depth of new information has been minimal. One explanation may be that immunization service delivery by the private sector has not been a priority area for immunization programs. Additionally, studies have often focused on an individual vaccine, or a geographic area within a country, providing a limited picture. Furthermore, information about the role of the private sector may be embedded in publications on overall immunization system performance, practices to improve coverage of a specific vaccine, or in a general analysis of private sector healthcare delivery. Thus, all information relevant to this study may not have been captured in a literature review targeting private sector engagement as it pertains to immunization services.

Furthermore, scant information from high-income countries was identified. Conceivably, in high-income countries where private sector delivery is predominant, the public-private model of collaboration has not been evaluated because its effectiveness and functionality is not in question. Infrastructure is already in place to operate within the scope of immunization best practices and high coverage rates have been achieved. Therefore, our review was somewhat limited to a qualitative descriptive review rather than a quantifiable assessment. While findings have been elucidated, they do not capture all the dimensions at play, cannot be generalized between countries, and limit comparisons between the two sectors. Extending qualitative interviews to representatives of the International Paediatric Association and other organizations and private providers could further inform the issue of private sector engagement.

VI. Conclusion

Evidence remains limited about the private sector's contribution to immunization services, impact on equity of immunization services, and interaction between the pharmaceutical industry and private sector and too few surveys and studies of the current or potential contribution of the private sector to NIPs have been conducted. Based on limited sources of information we were able to identify that while there are a number of countries that have successfully engaged with the private sector and used it as a platform to improve their immunization programmes, others have minimal involvement or have experienced challenges.

There needs to be increased collaboration between private sector providers and the NIP. In a significant portion of the LMICs included in this study, private sector immunization services were not as efficient or accountable as their public sector counterparts. While NIPs may not have the financial and staffing resources to support private providers, private providers would benefit from their subject matter expertise and best practice guidelines until mechanisms are established at the national level. It is not until private sector immunization delivery is strengthened and regulated that their services can support progress towards GVAP goals.

In order to productively engage the private sector for immunization service delivery there needs to be an increased collaboration between private sector providers and NIPs, several steps could be pursued. This could start with a review of the private sector contribution to immunization delivery as well as programme monitoring and adverse events and disease surveillance, and a look into the quality of service delivery and an effort to identify and inventory key stakeholders in private sector involved or that could be potentially involved in vaccination. This could then be followed by determination of optimal model of public private engagement and develop or expand collaboration and dialogue to achieve common immunization goals and development of collaborative activities and potentially memorandum of understanding, agreements or contracts. Clearly there is a need to put in place mechanisms to allow for some regulation and quality control of the immunization service delivery and importantly to ensure exchange of information between the public and the private sector as well as training and capacity building of private providers.

Utilization of the private sector for immunization delivery should be placed in the context of health system strengthening and Universal Health Coverage (40). In August 2016, the Lancet published a four article series on the performance of private sector health care in LMICS. Morgan et al. noted that deriving population benefit from the private sector requires interventions that target the sector as a whole rather than individual providers or specific services (41). By anchoring this topic in the continuum of care and sustainable health outcomes the policy dialogue at the national level may have more traction. Thus, it may gain further buy-in to adapt to changes in service delivery partners, programme design, and expectations.

Furthermore, expanding the current body of evidence is essential to elucidate characteristics of a well-functioning immunization program. Areas that need to be highlighted as a research priority include: 1) private sectors role in geographic scope leading to forecasting demand and stock-outs; 2) effectiveness of regulatory requirements and potential enforcement mechanisms; 3) best practices for incorporation of private sector provision of immunization services into the NIP; 4) identification of where private providers are securing vaccines and if vaccines are licensed. Additionally, the role of immunization delivery in private schools was not captured and should be addressed as a priority area given centrality of school-based immunization programs to meet coverage targets and compliance with national schedules. Through these mechanisms and extension of research, the interaction between public and private sectors can be optimized and immunization services can be strengthened to meet the goals laid forth by GVAP.

Figure I: Results from Literature Search and Review Process

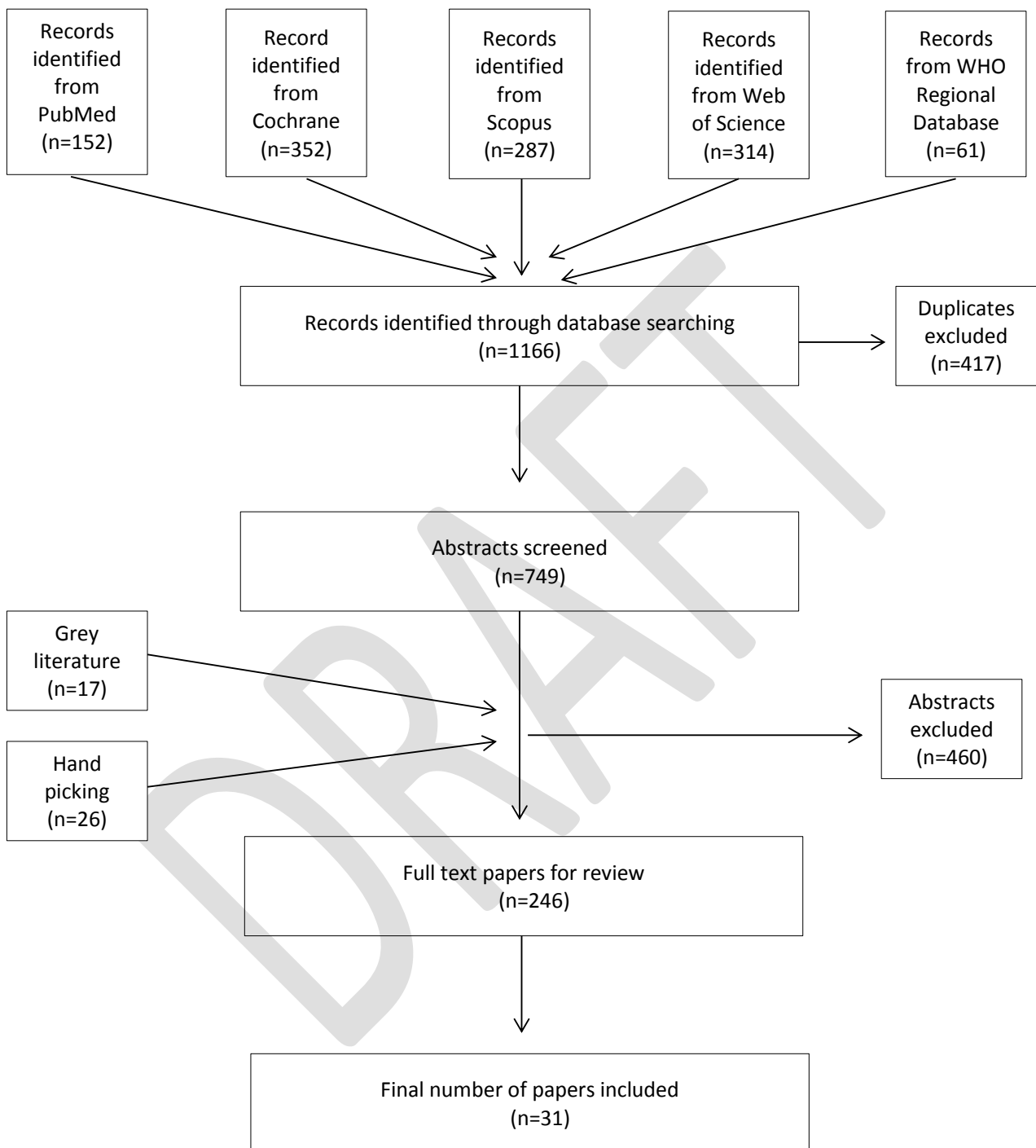


Table I: Immunization Experts included in Semi-Structured Interviews, by affiliation, country and WHO region, 2016

Name	Affiliation	Country	WHO Region
Dr José Ignacio Santos	National Autonomous University of Mexico	Mexico	AMR
Dr Monique Landry	Ministère de la Santé et des Services sociaux du Québec	Canada	AMR
Dr Jaleela S. Jawad	Ministry of Health, Bahrain	Bahrain	EMR
Dr Alissar Rady	World Health Organization, Lebanon	Lebanon	EMR
Dr Ole Wichmann	Robert Koch Institut, Berlin	Germany	EUR

Table II: Literature included in Final Analysis, by country, WHO region, classification and topic area, 2016.

Source	Country	WHO Region	Country's Economic Classification	Topic Area
Articles/Reports				
Amarasinghe 2016	Western Pacific Region	WPR	-	Program monitoring & post market surveillance
Ategbo et al. 2011	Gabon	AFR	Upper-middle	Vaccine share
Babirye et al. 2014	Uganda	AFR	Low	Vaccine share, quality standards, equity
Basu et al. 2012	Systematic Review	-	-	Quality standards, equity, private sector healthcare
Boulianne, N. et al. 2015	Canada	AMR	High	Vaccine share
Cho et al. 2010	Republic of Korea	WPR	High	Vaccine share, decision-making
Dominguez et al. 2007	Spain	EUR	High	Vaccine share
Groom et al. 2007	United States	AMR	High	Vaccine share, program monitoring & post market surveillance, equity
Hagan et al. 2016	India	SEAR	Lower-middle	Vaccine share, program monitoring & market surveillance
Irons & Dobbins 2011	Caribbean	AMR	-	Vaccine share
Lahariya et al. 2013	India	SEAR	Lower-middle	Program monitoring & post market surveillance
Levinson, D. 2012	United States	AMR	High	Vaccine share, quality assurance
Mackintosh et al. 2011	-	-	-	Private sector healthcare
Makinen et al. 2011	Ghana	AFR	Low	Vaccine share
Morgan et al. 2016	-	-	-	Private sector healthcare
Murakami et al. 2008	Vietnam	WPR	Middle	Vaccine share
O'Flanagan et al. 2011	EU/EAA	-	-	Vaccine share
Oluoha, C., Umeh, C. Ahaneku, H., 2014	Nigeria	AFR	Lower-middle	Vaccine share, quality standards, decision-making
Orenstein et al.	United States	AMR	High	Vaccine share, quality standards,

Source	Country	WHO Region	Country's Economic Classification	Topic Area
2005	States			program monitoring & post market surveillance, decision-making
Patel et al. 2014	Philippines	WPR	Lower-middle	Vaccine share, quality standards, program monitoring & post market surveillance
Pavlopoulou et al. 2013	Greece	EUR	High	Vaccine share
Sharma et al. 2015	India	SEAR	Lower-middle	Vaccine share, equity
Sharma et al. 2016	India	SEAR	Lower-middle	Vaccine share, equity
Soeung et al. 2008	Cambodia	WPR	Lower-middle	Vaccine share, quality standards
Sood, N. & Wagner, Z., 2013	Kenya	AFR	Lower-middle	Vaccine share, equity
Uddin et al. 2012	Bangladesh	SEAR	Low	Vaccine share
Vaccine European New Integrated Collaboration Effort 2006	France	EUR	High	Vaccine share
Wagner et al. 2014	Sub-Saharan Africa	AFR	-	Vaccine share, equity
Whitney et al. 2014	United States	AMR	High	Quality standards
Zaidi et al. 2015	Pakistan	EMR	Low	Vaccine share
Zaidi 2012	Pakistan	EMR	Low	Vaccine share
Personal Communication				
J Jawad 2016	Bahrain	EMRO	High	Vaccine share, quality standards, program monitoring & post market surveillance, decision-making, equity, interaction with pharmaceutical industry
M Landry 2016	Quebec, Canada	AMRO	High	Vaccine share, quality standards, advocacy, program monitoring & post market surveillance, decision-making
A Rady 2016	Lebanon	EMRO	Upper-middle	Vaccine share
J Santos 2016	Mexico	AMRO	Upper-middle	Vaccine share, program monitoring & post market surveillance, decision-making
L Suy 2016	Philippines	WPRO	Lower-middle	Vaccine share, program monitoring & post market surveillance
O Wichmann 2016	Germany	EURO	High	Vaccine share, advocacy, program monitoring & post market surveillance, decision-making, equity, interaction with pharmaceutical industry

Table III. Proportion of private providers providing vaccination services and proportion of vaccinations provided by private providers, by World Health Organization (WHO) Region as reported in publications and expert interviews.

Country (year data collected)	% Private providers providing vaccinations	% Vaccinations provided by private providers	Source	Comment
WHO African Region				
Kenya (2010)	34 (for profit), (80 not for profit)		Sood & Wagner, 2013	Odds of not being vaccinated 4.8 times higher where facilities are for-profit compared to areas with no for-profit facilities. Modelling from DHS, SPA surveys.
Nigeria, Abia State, 4 LGAs, urban, peri-urban (2011)		21	Oluoha et al, 2014	Monthly administrative data; 45% of facilities offering vaccine were private.
Uganda, Kampala (2010)		30	Babirye et al. 2014	30% respondents reported using for-profit providers
WHO South-East Asia Region				
India total (2009)		9	UNICEF Coverage Survey 2009	Household survey;% partially/fully immunized in private sector
India urban		21	"	"
India rural		6	"	"
India, 16 states.>90% India birth cohort.(2009-12)		5 (BCG)	Sharma et al. 2016	Estimate based on sales data. Weighted mean. Range 1 (Bihar)-17 (Punjab-Haryana)
		4 (Measles)	"	Range 1 (Assam)-19 (Kerala)
		2 (DTP3)	"	Range 1 (Orissa) - 7 (Kerala)
		4 (OPV)	"	Range 0.1 (W Bengal-82 (Kerala) OPV3> actual due to likelihood of >4OPV doses/child
Bangladesh, Dhaka city		4 (Hib)	Sharma et al. 2015	
		95	Uddin et al. 2012	
WHO Western-Pacific Region				

Philippines		10	L Suy 2016	Estimate from interview
Republic of Korea	60		Cho et al. 2010	
Cambodia	65 (provided at least 1 antigen)		Soeung et al. 2008	% of for-profit facilities offering specific antigens: 56 (HepB), 35 (tetanus), 10 (BCG), 4 (DTP), 4 (measles), 36 (rabies), 12 (typhoid), 10 (JE)
WHO Eastern Mediterranean Region				
Bahrain		<10	J Jawad, 2016	Estimate from interview
Lebanon		60 (for profit 40 (not for profit)	A Rady 2016	Estimate from interview
Pakistan		97	Zaidi 2012	Zaidi A. Evaluation of GAVI Support to CSOs: Country Evaluation Report -2012
Pakistan (Karachi)		25	Zaidi 2012	
WHO Region of the Americas				
Caribbean		10-20	Irons & Dobbins 2011	
Mexico		5	J Santos 2016	Estimate provided in interview
Quebec, Canada		20	M Landry 2016	Estimate provided in interview
United States		61- exclusively in private 23-combination public/private	Groom et al. 2007	61% children vaccinated exclusively in private sector; 23% combination of public and private
WHO European Region				
Catalonia, Spain (2003-4)		31 (EPI series) 63 (varicella) 47 (PCV7) 52 (Hep B)	Borras et al, 2009	Telephone survey of parents of 3 yr-olds. No difference in coverage (basic series+booster), 88% for both private and public
Germany		90	O Wichmann 2016	Estimate from interview
Greece		33	Pavlopoulou et al. 2013	

		90	O'Flanagan et al. 2012	Estimate reported in survey of vaccine program managers (children <3 yrs)
Austria				
Belgium		20	"	"
Cyprus		57	"	"
Czech Republic		95	"	"
France		90	"	"
Greece		70	"	"
Hungary		<1	"	"
Ireland		100	"	"
Latvia		1	"	"
Luxembourg		100	"	"
Malta		10	"	"
Poland		5	"	"
Romania		10	"	"

References

1. World Health Organization. Global Vaccine Action Plan. *Vaccine*. 2011;1–147.
2. Levin A, Kaddar M. Role of the private sector in the provision of immunization services in low- and middle-income countries. *Health Policy Plan*. 2011;26(SUPPL. 1):4–12.
3. Sood N, Wagner Z. For-profit sector immunization service provision: Does low provision create a barrier to take-up? *Health Policy Plan*. 2013;28(7):730–8.
4. Basu S, Andrews J, Kishore S, Panjabi R, Stuckler D. Comparative performance of private and public healthcare systems in low- and middle-income countries: A systematic review. *PLoS Med*. 2012;9(6).
5. Ategbro et al. Immunization coverage of children aged 0 to 5 years in Libreville (Gabon). *Sante*. 2011;20(4):215–9.
6. Oluoha C, Umeh C, Ahaneku H. Assessing the contributions of private health facilities in a pioneer private-public partnership in childhood immunization in Nigeria. *J Public Health Africa*. 2014;5(1):40–2.
7. Babirye JN, Engebretsen IMS, Rutebemberwa E, Kiguli J, Nuwaha F. Urban settings do not ensure access to services: findings from the immunisation programme in Kampala Uganda. *BMC Health Serv Res*. 2014;14(1):111.
8. Wagner Z, Szilagyi PG, Sood N. Comparative performance of public and private sector delivery of BCG vaccination: Evidence from Sub-Saharan Africa. *Vaccine*. 2014;32:4522–8.
9. Makinen M et al. Private Health Sector Assessment in Ghana [Internet]. World Bank Working Paper. 2011. Available from: <http://www.resultsfordevelopment.org/sites/resultsfordevelopment.org/files/R4D Private Health Sector Assessment in Ghana.pdf>
10. Sharma A, Kaplan WA, Chokshi M, Zodpey SP. Role of the private sector in vaccination service delivery in India: evidence from private-sector vaccine sales data, 2009–12. *Health Policy Plan*. 2016;31(7):884–96.
11. Uddin MJ, Saha NC, Islam Z, Khan IA, Shamsuzzaman, Quaiyum MA, et al. Improving low coverage of child immunization in rural hard-to-reach areas of Bangladesh: Findings from a project using multiple interventions. *Vaccine* [Internet]. Elsevier Ltd; 2012;30(2):168–79. Available from: <http://dx.doi.org/10.1016/j.vaccine.2011.11.030>
12. Sharma a, Kaplan W a, Chokshi M, Hasan Farooqui H, Zodpey SP. Implications of private sector Hib vaccine coverage for the introduction of public sector Hib-containing pentavalent vaccine in India: evidence from retrospective time series data. *BMJ Open*. 2015;5.
13. Cho H, Kim C, Go U, Lee H. Immunization decision-making in the Republic of Korea : The structure and functioning of the Korea Advisory Committee on Immunization Practices. *Vaccine* [Internet]. Elsevier Ltd; 2010;28:A91–5. Available from: <http://dx.doi.org/10.1016/j.vaccine.2010.02.040>
14. Suy LL, Director, Disease Prevention & Control Bureau R of PD of H. Personal Communication. 2016.
15. Patel MK, Capeding RZ, Ducusin JU, de Quiroz Castro M, Garcia LC, Hennessey K. Findings from a hepatitis B birth dose assessment in health facilities in the Philippines: Opportunities to engage the private sector. *Vaccine*. 2014;32:5140–4.
16. Murakami H, Van Cuong N, Huynh L, Hipgrave DB. Implementation of and costs associated with providing a birth-dose of hepatitis B vaccine in Viet Nam. *Vaccine*. 2008;26(11):1411–9.
17. Soeung SC, Grundy J, Morn C, Samnang C. Evaluation of immunization knowledge, practices, and service-delivery in the private sector in Cambodia. *J Heal Popul Nutr*. 2008;26(1):95–104.
18. Zaidi A. Evaluation of GAVI Support to Civil Society Organisations: Country Evaluation Report - Pakistan. 2012.
19. Zaidi S, Riaz A, Rabbani F, Azam SI, Imran SN, Pradhan NA, et al. Can contracted out health facilities improve access, equity, and quality of maternal and newborn health services? Evidence from Pakistan. *Heal Res Policy Syst. Health Research Policy and Systems*; 2015;13(1).
20. Jawad, Jalilah, Head of Vaccination, Ministry of Health B. Personal Communication. 2016.
21. Rady, Alissar, National Professional Officer, World Health Organization L. Personal Communication.

- 2016.
22. Groom H, Kolasa M, Wooten K, Ching P, Shefer A. Childhood immunization coverage by provider type. *J Public Heal Manag Pract.* 2007;13(6):584–9.
 23. Santos, Jose Ignacio, Professor, School of Medicine, National Autonomous University of Mexico M. Personal Communication. 2016.
 24. Irons B, Dobbins JG. The Caribbean experience in maintaining high measles vaccine coverage. *J Infect Dis.* 2011;204(SUPPL. 1).
 25. Levinson DR. Vaccines for Children Program: Vulnerabilities in Vaccine Management. 2012.
 26. Orenstein WA, Douglas RG, Rodewald LE, Hinman AR. Immunizations in the United States: Success, structure, and stress - A complex collaboration involving government, industry, providers, academe, professional societies, and third-party payers. *Health Aff.* 2005;24(3):599–610.
 27. Landry, Monique, Medical Advisor, Public Health Directorate, Ministry of Health and Social Services of Quebec C. Personal Communication. 2016.
 28. Boulianne N, Audet D, Ouakki M. Enquête sur la couverture vaccinale des enfants de 1 an et 2 ans au Québec en 2010 [Internet]. 2015. Available from: https://www.inspq.qc.ca/pdf/publications/1973_Enquete_Couverture_Vaccinale_Enfants.pdf
 29. O’Flanagan, Darina, Cotter, Suzanne, Mereckiene J. Vaccination coverage assessment in EU/EEA, 2011. 2012.
 30. Dominguez A, Oviedo M, Batalla J, Salleras L, Borrás E. The influence of public or private paediatric health care on vaccination coverages in children in Catalonia (Spain). *Eur J Public Health.* 2008;19(1):69–72.
 31. Pavlopoulou ID, Michail KA, Samoli E, Tsiftis G, Tsooumakas K. Immunization coverage and predictive factors for complete and age-appropriate vaccination among preschoolers in Athens , Greece : a cross- sectional study. *BMC Public Health.* 2013;13(908):1–10.
 32. Vaccine European New Integrated Collaboration Effort. France Immunization Delivery [Internet]. 2006. Available from: http://venice.cineca.org/documents/france_ip.pdf
 33. Wichmann, Ole, Head, Immunization Unit, Department of Infectious Disease Epidemiology, Robert Koch Institute G. Personal Communication. 2016.
 34. Whitney C et al. Benefits from Immunization During the Vaccines for Children Program Era - United States, 1994–2013. *Morb Mortal Wkly Rep.* 2014;63(13):352–5.
 35. Lahariya C, Subramanya BP, Sosler S. An assessment of hepatitis B vaccine introduction in India: Lessons for roll out and scale up of new vaccines in immunization programs. *Indian J Public Health.* 2013;57(1):8–14.
 36. Hagan, J et al. (2017) *Knowledge, Attitudes, and Practices of Private Sector Routine Immunization Providers in Gujarat, India.* Manuscript submitted for publication.
 37. Amarasinghe DA (Western PRO. Survey on private providers’ engagement in immunization in Western Pacific Region: preliminary findings. *Pers Commun.* 2016;
 38. Centers for Disease Control and Prevention. Advisory Committee on Immunization Practices (ACIP) [Internet]. 2016 [cited 2016 Sep 24]. Available from: <https://www.cdc.gov/vaccines/acip/about.html>
 39. Mackintosh M, Channon A, Karan A, Selvaraj S, Zhao H, Cavagnero E, et al. What is the private sector ? Understanding private provision in the health systems of low-income and middle-income countries. *Lancet.* Elsevier Ltd; 2016;6736(16):1–10.
 40. World Health Organization. Weekly epidemiological record Relevé épidémiologique hebdomadaire. 2008;21(83):421–8.
 41. Morgan R, Ensor T, Waters H. Performance of private sector health care : implications for universal health coverage. *Lancet.* Elsevier Ltd; 2016;6736(16):1–7.

WHO Guidance Note: Engagement of private providers in immunization service delivery. Considerations for National Immunization Programmes

Contents

1. Introduction and aims	2
2. Background and definitions.....	3
3. Considerations related to the engagement of the private sector in national immunization programmes ...	4
3.1 Contribution to vaccination service delivery and coverage	4
3.2 Immunization practices, service quality, and missed opportunities.....	5
3.3 Vaccination schedule	6
3.4 Equity of services	6
3.5 Advocacy	7
3.6 Programme monitoring, coverage reporting and disease and adverse event surveillance	7
3.7 Private providers' role in policy and decision-making	8
3.8 Private sector interaction with manufacturers.....	9
4. Framework for engaging the Private Sector to Support National Immunization Programmes	9
4.1 Assessment of private providers in immunization service delivery.....	9
4.1.1 Review existing information about the private sector contribution to immunization coverage, adverse events and disease surveillance, and service quality issues.	9
4.1.2 Identify and inventory key stakeholders in private sector involved or potentially involved in vaccination	9
4.2 Determination of optimal model of public private engagement.....	10
4.3 Development or expansion of collaboration and dialogue to achieve common immunization goals.....	10
4.4 Development of collaborative activities, agreements and contracts	11
4.5 Training and capacity building	12
4.6 Regulation, standards and quality control.....	12
5. Recommendations.....	14
References.....	17
Table 1. Proportion of private providers providing vaccination services and proportion of vaccinations provided by private providers, by World Health Organization (WHO) Region as reported in publications and expert interviews.....	18
Table 2. Summary of studies comparing vaccination coverage by private and public providers, as reported in literature	22
Figure 1. Proportion of countries with >50% Private Expenditure on Health of Total Expenditure by WHO Region and Income Level (n=192)	23

1. Introduction and aims

Vaccinations are a core component of the human right to health, preventing communicable disease at the individual and population levels. In 2012, the World Health Assembly adopted the Global Vaccine Action Plan (GVAP) with the goal of providing equitable access to vaccines by 2020 (1). The GVAP sets ambitious goals that may only be attainable through shared responsibility and partnerships of the various groups that are involved in providing healthcare. One of the recommendations to achieve its strategic objective 4 (i.e. Strong immunization systems that are an integral part of a well-functioning health system) is to: “*Ensure coordination between the public and private sectors for new vaccine introduction, reporting of vaccine-preventable diseases and administration of vaccines, and ensure quality of vaccination in the public and private sectors*”. Furthermore, the global routine immunization strategies and practice (GRISP) a companion document to the GVAP (3), recommends activities to: *Enable and harmonize routine immunization services provided by the private and nongovernmental sector*. Healthcare systems in countries involve different combinations of public and private funding and delivery models. In April 2016, the WHO’s Strategic Advisory Group of Experts on Immunization (SAGE) stressed that the implementation of immunizations in the context of health system strengthening and Universal Health Coverage¹ requires integration between various healthcare sectors.

Indeed, successful implementation and reaching the goals of the GVAP and necessary improvements in vaccine coverage rates at all levels require the optimization of the interaction between public and private (for-profit and not-for-profit) healthcare sectors. The challenge of national vaccination programmes (NIPs) is to achieve the goal of high vaccination coverage and reducing equity gaps, often in resource-constrained settings. Engagement with the private sector to optimize effective vaccination services, has the potential to help improve the programme and increase coverage, but only if the roles are clearly defined and the services are collaborative with the existing health system and standards (4, 5). In countries where there is both public and private immunization delivery, there is often variation in coverage and accessibility of providers. The variation can be geographic and/or related to socioeconomic and/or insurance status (4, 5). As each country performs differently, and is faced with a myriad of characteristics that make it unique, a single standard approach to engaging the private sector is not realistic or appropriate. The role of the private sector (contribution to coverage, service quality, disease and adverse events following immunization (AEFI) surveillance), and its engagement with national immunization programmes varies within and between countries and remains poorly understood (4–6). This applies not only to the direct contribution of the private sector to the delivery of vaccines and the provision of health care, but also to the interaction between sectors, its impact on equity of services, level of monitoring, and degree of regulations on private providers.

¹ Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicine and vaccines for all.

This guidance note aims to:

- 1 Present considerations related to private providers involved in vaccine delivery, including potential contributions to coverage (including equity issues), vaccination practices and service quality, program monitoring, and safety and disease surveillance reporting.**
- 2 Propose a framework for facilitating the engagement of private providers, and**
- 3 Provide recommendations to support optimal engagement of private providers in immunization service delivery.**

Although recommendations are provided, recognizing the need to adapt to the specific country circumstances, the document does not intend to prescribe the type of engagement of the private providers. It does not attempt to quantify the impact of the private sector itself or create a hierarchy proposing that one system of delivery (i.e. private, mixed, or public model) is better than another. The intent is not to advocate for a greater or smaller role of the private sector in health care, but for a closer collaboration between the public and private sectors and a stronger contribution of the private sector toward national immunization programme priorities.

2. Background and definitions

A broad definition describes the private sector as, “comprising all health care providers who exist outside of the public sector, whether their aim is for philanthropic or commercial purposes” (7,8). However, there is a need to further differentiate provision and financing of health services outside of the public sector as there can be considerable overlap (5,8). In some cases, a system can be funded by the public sector through a national healthcare system, but care provided by the private sector. There are also systems that are funded by private insurance, but with care provided by public providers. Additionally, a system can exist that is dependent on a mixed-scheme of public and private funding and public and private providers as typically seen in most lower and middle income countries (LMICs) (5). This document considers the provision of vaccination and other health services provided by any entity outside of the government either by an individual or by an institution. This encompasses full-time or part-time private practitioners, private for-profit and not-for profit primary care organizations and hospitals, civil society organizations (CSOs), non-governmental organizations (NGOs), faith-based organizations (FBOs), community-based organizations (CBOs), and private companies such as mining or other large industries that provide internal medical services for their employees and their families (5). Not included in the scope of this document are the private vaccine and vaccine delivery technologies manufacturing industries, and private practitioners in the informal sector (e.g., traditional healers and informal drug retailers).

Private sector engagement (PSE) can be defined as the deliberate, systematic collaboration of the government and the private sector to move national health priorities forward, beyond individual interventions and programs(9). The process of PSE has been described for vaccine supply chains, and engagement guidance documents specific to that process have been developed (9,10), but guidance on other aspects of immunization service delivery has not been developed. Private sector health services exist in all countries to some degree, and government engagement with the private sector is underway in all countries, to variable degrees. A variety of models are being utilized to deliver immunization services between public and private providers. In some countries, FBO-managed or NGO-managed hospitals are integrated and at times nearly indistinguishable from the public sector (11). In the majority of LMICs, publicly funded immunization services are provided by public providers but in many countries private providers also contribute to the delivery of these services

(5). Private providers can work full-time in the private sector or be based out of the public sector and serve as part time private service providers. Private providers may also provide services in school and occupational health settings (12). Many high-income countries rely on private providers as their primary means for immunization delivery with established health insurance schemes. Increasingly, LMIC countries are also using the private sector to deliver core health care services funded by Universal Health Coverage programs (5,6). The private sector is sometimes perceived as serving the wealthy, but this is not strictly true. Private sector providers, including for-profit and FBOs and NGOs, often provide services to poor and rural underserved populations (5).

PSE in the health system has been shown to add value at various levels, including increased access to skills and expertise, operational efficiencies, increased innovation, shared risk, and allowing the government to focus on its core competencies (9). PSE is particularly important in LMICs, where government resources may lack the capacity to achieve national health and vaccination goals (11). More effective engagement between the public and private health care sectors in terms of better policies, regulations, information sharing, and financing mechanisms, could improve the performance of health systems (12).

There are a number of reasons why one may seek immunization services from the private sector. Immunization services may be more convenient given proximity to a private provider as frequently seen in urban densely populated locations (4). People may consider immunization services to be of better quality with increased efficiency (e.g. shorter wait times) when delivered by a private provider even if the service incurs a fee (4,11). Also, in a growing number of countries, the private sector is used by a fraction of the population who wish to have access to vaccines not provided in the national schedule (see below for further details) (4). While in some countries the use of the private sector is limited to a small portion of the population such as the wealthy, expatriates, and employees of large corporations, or people in large cities, in other countries there is an increasing share of health delivery occurring in this sector (4,5).

The NIP in countries typically leads immunization service delivery with varying contributions from the private sector. In most lower and middle income (LMIC) countries, the NIP is part of a basic public package of health services provided and financed by the government, often supplemented by international donors. A country's ability to deliver these services is affected by its economic level and governance capacity (4). Frequently, in low income countries, the ability to provide preventative services is challenged by financial constraints, a limited health infrastructure, and competing health priorities (5,12).

3. Considerations related to the engagement of the private sector in national immunization programmes

There are several considerations related to private providers involved in vaccine delivery. Limited information only exists for several of these considerations, and is summarized below.

3.1 Contribution to vaccination service delivery and coverage

Provision of health care by private providers

Standardized country-specific information about the *share of overall health expenditures* in the private sector shows that the private sector has a major role in health care delivery. For example in 2014, the proportion of private sector share total expenditure on health care exceeded 20% in 82%

of 192 countries globally and exceeded 50% in 30 % of countries², with large variation by WHO region and country income status (Figure 1). However, overall expenditures include those for curative care, which outweigh preventive care expenditures. Participation of the private sector in *preventive services* (most commonly vaccination and prenatal care) is usually more limited. For example, in Africa, private sector participation in preventive services was 45 percent in Nigeria, 30 percent in Uganda, but less than 20 percent elsewhere (13). FBOs and NGOs are the main providers of private activity, often in partnership with the public sector (13).

Provision of vaccination services by private providers

Relative to the contribution of private providers to immunization service delivery specifically, currently available data do not allow for a comprehensive quantification. The location of vaccination (private vs public sector) is not captured in demographic health surveys (DHS). Service provision assessment (SPA) health facility surveys include both public and private facilities, enabling some comparison of vaccination service delivery characteristics by public and private ownership categories (14). However, vaccination coverage is not included, and SPAs have been done in a limited number of countries. Thus the private sector contribution to vaccination service delivery remains largely unknown, as noted in both the 2011(4) and more recent review (5), and is limited to a small number of studies. The proportion of private providers that offer vaccination services varies across countries (Table 1). Generally, the proportion of private for-profit facilities offering vaccinations is lower than the proportion of private not-for-profit facilities (14). The proportion of vaccines provided by the private sector also varies widely (Table 1). The limited number of studies that compared vaccination coverage between private and public sectors used different methodologies and found both lower, higher or no difference in coverage (Table 2).

3.2 Immunization practices, service quality, and missed opportunities

A previous review found that the few studies (in Cambodia, Mauritania and Malaysia) that addressed quality of vaccination service delivery by private providers in vaccination delivery in low- and middle-income countries generally found suboptimal immunization practices and knowledge levels among private sector providers (4). More recent studies that addressed these issues are limited in number, but likewise found service quality issues. However systematic assessments that compare vaccination practices among private and public sectors over a larger number of countries are lacking. A recent study of the knowledge, attitudes, and practices of private immunization providers (paediatricians and general practitioners) in urban settings in Gujarat, India, identified several practices with safety and quality concerns and practices potentially leading to missed opportunities for vaccination (MOV). Cold-chain quality varied greatly. In almost all cases, vaccines were stored in domestic refrigerators and some stored vaccine vials in unrefrigerated thermal boxes. Expired vaccine vial monitors were noted in 18% of observed refrigerators. Vaccine schedules were not strictly followed by 45% of participants if there were concerns about ability to pay, and 60% of practitioners responded that they do not administer more than two injections in the same visit. Half of the providers responded that they would not vaccinate a child who presented for immunizations without their home-based vaccination card and half reported that they would not administer

² Analysis using Global Health Observatory data, available at <http://www.who.int/gho>

vaccines if the child was mildly ill. Few (22%) providers used a vaccine register to record vaccine doses, rendering identification of defaulters difficult (15).

Surveys in representative samples of 3,219 health facilities in four African countries (Kenya, Malawi, Senegal, Tanzania) found barriers to vaccination and missed opportunities in both private and public health facilities (14). A smaller proportion of for-profit facilities offered child vaccination services (country range, 25-37%) than did public facilities (range, 90-96%). Less than a third of for-profit facilities offered measles vaccination daily. A minority of both private and public providers assessed the child's vaccination status during a sick child visit (range by country and facility type, 14-44%), or offered tetanus toxoid during antenatal visits (range, 19-51%). Among for-profit providers, 18-32% (range across countries) assessed the child's vaccination status during a sick child visit.

3.3 Vaccination schedule

A private provider's choice of routine vaccines and administration schedule should follow those dictated by their country's national scheme. However, private providers administering vaccines outside of a contractual agreement may choose to offer different vaccines or utilize new ones that have yet to be introduced by the Ministry of Health (MOH) (5). The for-profit sector is often targeted by vaccine manufacturer marketing campaigns for new vaccines. New vaccine introduction in the private sector can place pressure on the public sector to introduce these vaccines into the NIP (5). Besides being incentivized by vaccine manufacturers to offer new vaccines, private providers may also feel market pressures to meet the requests of the client e.g., when the client requests a new vaccine, an alternate schedule or expatriates request schedules used in their own countries. While some countries have started to penalize public physicians who deviate from the recommended national schedule, this type of control can be difficult to extend to the private sector and its impact has yet to be documented (5).

Modifications to vaccination schedules and use of different vaccines in the private sector have the capability to create epidemiological gaps which can lead to increased risks for the vaccine preventable diseases in populations not covered by the private sector (16). For example, the use of rubella-containing vaccines in a subset of the population without achieving high population immunity in the whole population can shift the overall risk of the disease to older ages (child bearing age women) where the complication rate for those not protected is higher. Further, there is a risk that different vaccine schedules being used by different providers may generate confusion, questioning and lack of trust by the population. Recently, despite a synchronized global withdrawal of OPV2 and switch from trivalent to bivalent OPV vaccine, use of trivalent OPV by some private physicians in India long after the switch was discovered, resulting in a global threat. Another potential source of confusion or mistrust is the use of full dose IPV in the private sector and fractional dose in the public sector in India, driven by IPV global shortages. Harmonization of vaccine use and schedules between sectors minimizes epidemiological gaps and risks and supports equity of services between sectors as well as the credibility of the programme.

3.4 Equity of services

Ensuring equitable access to immunization services is instrumental in achieving coverage goals. Equity not only applies to access, but also extends to vaccines that are only offered in the private sector, or where the private sector might use vaccines that offer different spectrums of individual protection than their public sector counterparts. Typically, private-for-profit services favour those in urban areas and of higher socio-economic status (5, 6,11). This has the potential to

create inequity if the poorest populations are unable to access public sector or NGO services. When immunization services are covered by the national insurance scheme, inequity poses less of a threat (6). In countries where immunization services are low performing and challenged by lack of infrastructure, contracting with NGO's has shown to decrease inequity by increasing access to services in the world's poorest, most vulnerable populations (3, 6). Areas with contracted NGOs are often seen to be positively associated with the likelihood of children being immunized regardless of household wealth (6).

Inequity can also be seen at the institutional level. Governments may favour the private sector due to the perception that private healthcare is more efficient than maintaining an exclusive public healthcare system (5). The private sector's involvement can potentially undermine the public sector by diverting public health sector financing to the private sector, reducing resources available in the public sector (6). In a country where a healthcare provider may be both a government and private provider, questions may arise concerning financial incentives for providers to defer vaccination in a public setting and refer their client to a fee-based immunization programme in a private setting. Issues of equity can also arise in a setting where the private sector reaches higher vaccination coverage rates in the population it serves because of financial incentives to the provider by an insurance company or vaccine manufacturing companies (6).

3.5 Advocacy

Health workers serve as an important source of information for parents. A health worker's perception of and communication about effectiveness and safety of vaccines is important in motivating them to encourage parents to vaccinate their children (17). If a provider, private or public, is unable to communicate the need for vaccination or lacks pertinent information, this will likely have a negative impact on vaccine uptake. Additionally, if immunization services are divided between two sectors and messages are divergent, this could contribute to a loss of public confidence and possible vaccine hesitancy (5). It has been noted that improper knowledge among private providers and hesitancy is greatest for new vaccines, administration of multiple vaccines in one visit, conjugate vaccines, and where more than one vaccine type (e.g. OPV versus IPV) is currently in use (5).

3.6 Programme monitoring, coverage reporting and disease and adverse event surveillance

Monitoring of vaccine coverage and disease and adverse event surveillance are key components of a vaccination program and should include the private sector. Collection, analysis, and interpretation of surveillance data guides vaccination policies and programmes to ensure GVAP immunization targets are being reached (5). Monitoring and supervision of private provider vaccination delivery and participation in adverse event and disease surveillance activities is often inadequate (4,5). For example, the study in urban Gujarat India found that a minority of private providers (31%) reported vaccine doses to the government, and providers commonly responded that they would not report AEFIs or cases that met surveillance definitions for vaccine preventable notifiable diseases, including measles and polio. The most common reason given was unawareness of any reporting requirement (15). Particularly in LMICs, monitoring and surveillance systems put in place through contractual agreements, are often insufficient with evident gaps in enforcement and adherence (6). In high-income countries where governments have infrastructure and mechanisms in place to capture this data, it is often left to the discretion of the provider, insurance company, or manufacturer to perform data collection (6).

Assessment of the contribution of the private sector to vaccination coverage rates in LMICs can be difficult as doses delivered are often unaccounted for and reporting to the government can be sporadic and not standardized (5). Published studies on the private provision of immunization services typically focus on an individual vaccine, most commonly hepatitis B and tetanus toxoid, or a defined geographical location providing only a limited picture of the situation (5). There is often also a lack of funding and support from the MOH for documentation and information management, despite its importance in system oversight and planning (18).

Inadequate reporting from the private sector has implications for loss of information on vaccines administered and thus on coverage and disease incidence, which can affect resource allocation (5). Additionally, inadequate reporting of AEFI can lead to underreporting and inaccurate post-market safety surveillance. Lack of reporting of vaccine preventable diseases impacts detection and investigation of selected disease syndromes affecting indicators for overall immunization programme performance (5). Even if the private sector is not directly delivering vaccines, they need to be engaged in vaccine preventable diseases surveillance and AEFI reporting to help address problems that may arise at the population level. Engaging private providers through professional associations, providing professional development support, immunization forums, and creating health-information communication linkages can support a collaborative relationship and build understanding between the two sectors.

3.7 Private providers' role in policy and decision-making

Currently, the majority of industrialized and many LMICs have formally established National Technical Advisory Groups (NITAGs) to guide immunization policies and decision-making while other countries are working towards forming these groups. NITAGs serve as both a technical resource and deliberative body to guide immunization policies and decision-making (19). NITAGs are made up of core members who should be independent and credible experts serving in their own capacity and who do not represent the interests of a particular group or stakeholder (19). A credible NITAG and related processes can have a very positive impact on perceptions about vaccination and the NIP, both within government but also among professional organizations, funders and the private sector and ensure a comprehensive and cohesive country immunization service delivery perspective (19). Representation of private sector partners through liaison members representing various professional organizations, insurers or individual experts serving as core NITAG members can be extremely beneficial (5,19). Liaison members do not participate in the decision making process but they can contribute to the discussion. Including private sector members in NITAGs can allow them to share their experiences and propose solutions to addressing the barriers to comprehensive vaccine coverage. When private sector representation is low on the NITAG, this can be a barrier to regular updating of knowledge pertaining to new scientific evidence, recommendations, and changes to policies due to the absence of a communication pathway (6). The NITAG can also serve as a means to seek formal agreements with private providers who deliver vaccines. Countries with professional bodies often have an established national advisory process to issue recommendations on vaccine use for their members (19). It is important to ensure close collaboration between these professional bodies and NITAGs to avoid conflicting recommendations that may undermine the credibility of both groups and to ensure uptake of, and adherence to, the national immunization schedule in both private and public health sectors (e.g. in the past those from the US National Academy of Paediatrics and Advisory Committee on Immunization Practices) (5,19).

3.8 Private sector interaction with manufacturers

Both the 2011 review and the more recent review of the private sector's in immunization found scant literature on the relationship between vaccine manufacturers and private providers (4, 5). It is known that the for-profit sector is often targeted by vaccine manufacturer marketing campaigns for new vaccines. Regulatory requirements and standard operating procedures should apply for both private and public sectors, including regulations for vaccines that are donated or offered "free" to the private sector (5). Additionally, it has been feared that some private providers may be reluctant for vaccine manufacturers to lower vaccine prices as this could result in decreased profit margins in settings where client charges are based on a percentage of vaccine costs.

4. Framework for engaging the Private Sector to Support National Immunization Programmes

Engagement with the private sector can improve the use and effectiveness of existing resources. Suggested steps for a strategy of the NIPs to engage private providers include the following:

4.1 Assessment of private providers in immunization service delivery

4.1.1 Review existing information about the private sector contribution to immunization coverage, adverse events and disease surveillance, and service quality issues.

Limited information about the private sector role in immunization delivery may exist, but may be available from administrative data (if private providers receive vaccine from the government), coverage surveys, facility surveys (e.g., service provision assessments) or specific studies. If private sector already provides a significant proportion of vaccinations, engagement could focus on service quality issues. If private sector providers do not contribute a significant proportion of vaccinations a potential role for them to expand the reach of the public sector could be considered.

4.1.2 Identify and inventory key stakeholders in private sector involved or potentially involved in vaccination

The NIP should identify and inventory the potential players and stakeholders from the private sector, e.g., "who is doing what and where", covering all aspects of the immunization programme (vaccine manufacture, import, procurement, education and social mobilization, vaccine programme delivery, to post-market surveillance including surveillance of vaccine preventable diseases and AEFIs). This exercise can be useful to foster conversations with private sector players to include in the engagement process and also to flag major system challenges relevant to private sector players and allow identification of policy reforms, system changes and potential activities that could address these challenges (11, 12). Governments could begin by initially targeting highly influential stakeholders who favour collaboration, then target stakeholders who are in favour but less influential, and finally, inform or co-opt those who are not in favour and are influential by keeping them informed (12).

4.2 Determination of optimal model of public private engagement

There are a number of countries that have engaged well with private providers and have used it as an engine to increase the reach of their immunization programme. Regardless of whether the public sector proactively engages with the private sector, the latter is already playing a role in immunization in most, if not all, countries (10). CSOs, NGOs and FBOs often play several roles in NIPs, e.g., education, advocacy, awareness raising and demand creation, resource mobilization, vaccine-preventable disease surveillance, provision of immunization services (11,18). In many LMIC countries these organizations, typically not-for-profit, have had longstanding arrangements with NIPs to provide vaccination services. Specific arrangements relative to technical and financial support vary. The government of Afghanistan contracts out the bulk of health service provision, including immunization, to CSOs. Health Net TPO, a health-focused NGO and key partner of the Ministry of Public Health in Afghanistan, runs the entire health system in 3 provinces (18). CSO leadership has been credited as playing a key role in the success of immunization coverage in spite of the country being ravaged by war (18). In a different type of arrangement vaccines are sourced by the MOH and then distributed to private providers for administration (5), an arrangement that has the advantage of increased control and standardization of the messaging about the vaccine. Providers report on the number of vaccines given, or participate in national immunization registries (4). This collaboration may stipulate that the private sector adheres to national standards of immunization service provision including reporting, monitoring, and quality service delivery (4, 6). Contracts that encompass technical support, or well-defined programme goals and consistent monitoring generally have a greater chance of producing higher coverage rates (3,4). Of note however, there is little information on the extent of government support to and successful arrangements with the private sector in LMICs. A survey of in Ghana and Kenya found that few private clinics reported receiving assistance for immunization service delivery. In Ghana, only 12% of private clinics, and in Kenya, only 20% reported financial or technical assistance from the government for childhood vaccinations (13).

High-income countries typically utilize the private sector to deliver the majority of their vaccinations and have mechanisms in place to capture vaccine coverage data (4). Private sector data is either submitted to the public sector at established time points, or to private physician associations who in turn report claims data to assess coverage (4). This leads to more complete information on vaccine coverage compared to LMICs, though gaps in reporting have been identified (4).

4.3 Development or expansion of collaboration and dialogue to achieve common immunization goals

In order to overcome preconceived misconceptions and biases between the public and private sector, private sector engagement must be approached in a way to maximise trust and predictability (11). Unpredictable policy changes, including changes in legislation, regulatory enforcement or subsidy allocations prevent long-term, scaled-up investments with the private sector (11). To build trust and foster dialogue, it is important to build engagement step by step through transparency, sharing united visions and long-term goals; with realistic expectations on both sides of relative contributions, capacities and timelines (9). Using approaches in change management can help alter attitudes and foster collaborative partnerships in PSE (20). Starting with small collaborative projects and building overtime, with the opportunity for quick wins to demonstrate progress, is part of this relationship-building process and allows partners to demonstrate commitment (9).

According to the World Bank's Healthy Partnerships guide, policy and dialogue are the foundations of effective private-public engagement (11). Meaningful dialogue between the public and private sectors around mutual goals, expectations and limitations is necessary to build trust and understanding (11). In order to foster collaborative engagement between the public and private sectors, there are 4 elements of good practice in policy and dialogue:

1. a high level of on-going implementation of engagement policy,
2. formally instituted dialogue mechanisms,
3. on-going dialogue between the government and the private sector, and
4. government policy to work with the private sector as a partner in the delivery of services (11).

In order to foster policy that supports PSE, many governments must revise existing immunization policy, or design new policies (12). Clarifying roles to support collaboration through policy frameworks may alleviate suspicion and mistrust between the government and the private sector, while improving effectiveness (12). The policy revision process involves developing public-private dialogue structures, identifying dialogue opportunities, and gaining stakeholder consensus (12). The opportunities for structured dialogue include participation in task forces, leadership committees, information sharing, and involvement in policy changes and prioritization (11). Involvement in task forces at various administrative levels allows private sector members to stay current with issues and play a part in offering solutions (21). One important way of collaborating with the private sector is its involvement in National Immunization Technical Advisory Groups (NITAGs).

4.4 Development of collaborative activities, agreements and contracts

One of the most important elements for engaging with the private sector in developing PSE policy, besides dialogue, is the development collaborative activities and formal agreements. National and regional immunization plans, programmes and strategies should not only be developed in collaboration with the private sector, but should also clearly articulate the private sector's role and expected contributions to both implementation and monitoring (21). Signed agreements, memorandums of understanding (MOU), or contracts can be developed between governments, development partners, and the private sector to formalize and clarify relationships, which can allow the private sector to expand their reach and contribution to immunization plans and programmes (21). This can be complex in view of the multiplicity of providers and it is clearly best if agreement can be negotiated with professional or umbrella organization. Governments may need to build capacity around contract development, negotiation and enforcement (9). MOUs are formalized statements of mutual expectations between two organizations or groups (22) MOUs can be useful for coordination of services: to specify services provided, facilitate communication processes, formalize partnership statuses, specify responsibilities and transfer authority within a partnership (22, 23). Contracts are more formal, and considered legally binding documents compared to MOUs. Contracts are one way for governments to collaborate with the private sector in order to achieve national vaccination goals (12). There are definite benefits of contracting the private sector to deliver various aspects of immunization services (9,13). Contractual agreements that encompass technical support, or well-defined programme goals with consistent monitoring, evaluation, as well as financial incentives, can be successful in producing high vaccination coverage rates (5). The private sector is more inclined to seriously consider collaboration and dialogue if there is a likelihood of being contracted to provide vaccination services (11). It is essential for all parties to enter contracts with clear expectations on performance, including performance measurement and consequences (9,20). However, contract development for PSE can be challenging. The contracting public sector needs to

know how to write, enforce and monitor a contract that includes important elements including payment terms, performance expectations, assessment, and contract renewal (9,20). The contract manager on the public side must be a senior official with project management experience, support and authority (20). There are practical toolkits available to help governments with the process of contracting (11). There is a tendency for governments to limit PSE to short-term contracts, such as 1 to 2 years in length, for various reasons including government funding cycles (9,20). However, this short time period is not long enough to allow for stable cash flow to justify the risk for many in the private sector (9,19). The other aspects that are necessary for successful PSE contracts are realistic key performance indicators, flexibility in allocation of resources, and payment (9). Further, appropriate contract oversight is necessary in order to ensure that deliverables are being met, issues are being resolved, and communication among stakeholders is effective (9). In some countries, NGOs and CSOs have umbrella organizations, platforms or coalitions representing multiple entities in the private sector that can participate in the PSE process (11,21). Coalitions also provide an opportunity for the private sector to shift some oversight responsibility from the government to the representative body (11).

4.5 Training and capacity building

Enhancing professional knowledge and skills through training and competency exams ensures accurate knowledge transfer and directly supports the success of immunization programmes and particularly the quality of the vaccination programme and its monitoring as well as disease surveillance. When providers have up-to-date information on changes in immunization theory, practice, and policy they can vaccinate safely and within their scope of practice (4). Training and quality standards not only apply to delivery mechanisms and immunization schedules, but extend to the safe and appropriate use of injections, proper vaccine storage and handling, screening for contraindications, proper recording, and safety surveillance.

Quality standards not only apply to vaccine information communication, but extend to the safe and appropriate use of injections including pain mitigation steps on immunization, proper vaccine storage and handling, screening for contraindications, proper recording, and safety surveillance. This also includes adhering to vaccine expiry dates. In most LMICs mechanisms to enforce quality standards for vaccine storage and administration in the private sector are limited due to human and financial resource constraints (4,5). NIP standards may only extend to contracted private sector services that have training and guidelines incorporated into their MOU (4,5). However, training accreditation and regulation does not have to be carried out by the government (11). In the Dominican Republic, INSALUD, a coordinating organization for more than 100 NGOs, participates in a National Commission for NGO Qualification and Accreditation, ensuring that NGOs receiving public funding are in compliance with requirements, standards and norms (11).

4.6 Regulation, standards and quality control

The three core aspects of regulatory functions include: registration and recording of new players in the health market, a quality regulatory framework for requirements of opening new facilities and inspections that do not discriminate between public and private, and effective enforcement of regulations (11). Regulations and standards can include (but are not limited to): vaccine schedules, licensing requirements, price controls, regulation of vaccines, regulation of private insurance, and fee waivers for those in poverty (12). Regulation can also require health professionals to attend continuing medical education (CME) before being able to renew their license

to practice (11). To be able to enforce regulation, governments must have a registry in order to know who is operating where (11). In many cases, professional self-regulation or third-party accreditation can relieve government of the burden of standards and enforcement (11). While the public sector is typically required to follow to the national schedule, without requirements the private sector may choose to offer different services based on a variety of factors including cost, supply, and client demand. One way this can manifest is when the client requests an alternate schedule or expatriates demand schedules used in their own countries (5,22). Some countries have started to penalize public physicians who deviate from the recommended national schedule, however, this type of control is difficult to extend to the private sector (5).

In most LMICs mechanisms to enforce quality standard for vaccine storage and administration are absent due to limited human and financial resources (4, 6). NIP standards only extend to contracted private sector services that have training and guidelines incorporated into their Memorandum of Understanding (MOU) (4, 6). In some settings, this can lead to private sector services being inferior to those administered in the public sector (4). Areas most commonly identified with breakdowns in quality standards include temperature chain management, immunization schedules, consent, and waste management (4,5,21). However, supply chain maintenance contracting with the private sector for the public sector has also had success and improved vaccination system efficiency (9,24). In the majority of high-income countries, infrastructure is in place to support private sector provision of vaccines (4). Here, information is more commonly exchanged between the public and private sector supporting quality standards and more frequent trainings and competency exams (16). There is a need to unify the standards between the public and private sector and for private providers to be routinely trained on immunization related topics to ensure even standards across sectors. Private providers can use a variety of mechanisms to procure vaccines and injection supplies through government channels or private suppliers and distributors. In some countries vaccines are sourced by MOHs and then dispatched to private providers for administration (5). There may be attempts from vaccine manufacturing industry to influence the private providers through advocacy promoting the use of their products even if not in agreement with the national immunization programme, unless it is carefully regulated.

Information disclosure and availability is essential in health systems planning, evaluation and surveillance, but currently in many countries the private system is not integrated or non-compliant with reporting (11). Reporting requirements must be reasonable, aligned with national priorities, and a single comprehensive system for both public and private sectors (11). There must be a legal requirement for the private sector to provide information to the government, and accountability systems to ensure that the data reaches the appropriate department (11). The private sector must be included in national vaccine coverage, vaccine preventable diseases and AEFI surveillance systems (11). Information must flow in both directions: data is collected and submitted to the government, and the government distributes regular surveillance, regulation and policy updates to the private sector (11,21). Currently information exchange between the public and private sector is weak in most countries, despite legal requirements existing in most (11). To strengthen reporting, the private sector can be involved in surveillance activities. The private sector must also be adequately trained to fulfil these tasks and be reimbursed for the investment of time.

Assessment of provider performance and feedback interventions are powerful strategies to improve vaccination practices and coverage.

5. Recommendations

NIPs should increase collaboration and communication with private providers delivering vaccination services regardless of the relative contribution of private providers to the delivery of vaccination.

Assess

- Countries should conduct an assessment of the current role of private providers in immunization service delivery, including their contribution to coverage, immunization advocacy, adverse events surveillance and vaccine preventable disease surveillance.
- An inventory of key players/stakeholders should be done to identify problems, strengths and challenges, and to identify what is needed to address the issues identified in the assessment.

Optimize service delivery

- The NIP should determine the optimal model for engagement with private sector that addresses identified issues and is tailored to the country immunization system (e.g., whether government supplies vaccines to private provider or not, existence and role of active professional bodies).
- The NIP should ensure that appropriate schedules and high-quality practices are implemented by private providers and that they are held to appropriate vaccine handling and storage standards. If vaccines administered in the private sector are provided by the public sector, they should be provided free of charge and private provider should comply with national reporting requirements and approved cold chain and vaccine handling practices. Measures should be taken to harmonize the private sector and government vaccination schedules ensure that all public and private vaccine providers are adhering to the national immunization schedule. This can be aided by having national vaccine procurement schemes, financial incentives through vaccine subsidy, capitalizing on the credibility of the NITAG and its involvement of the private sector, and appropriate communication.
- The NIP should consider feasibility of contracting portions of vaccination service delivery or supply chain to private providers to optimize capacity and efficiency, but this should be approached at a pace that minimizes risk.
- To prevent missed opportunities, private and public providers should use all clinical encounters to assess vaccination status and vaccinate clients as appropriate.
- Private providers should educate clients, parents, and guardians on the importance of vaccination and advocate for vaccination. Communication and advocacy efforts should align with and be supportive to the NIP.

Facilitate dialogue and decision making

- The NIP should provide the private sector with guidance on advocacy, AEFI and vaccine preventable disease reporting, and communication regarding immunization practices.
- Countries are encouraged to include private provider representation in NITAGs both as core members and as liaison members representing professional bodies and important NGOs.

This will support two-way communication flow and ensure that private sector issues are considered at the time when recommendations and policy guidance are being developed.

- Professional bodies and NITAGs should work with one another to ensure harmonized immunization schedules.

Ensure data management and reporting

- Governments or professional organizations should develop a database with information on all providers offering immunizations at the district and state level. The database should include the providers' contact information, list of vaccines provided, target population/catchment area, vaccine schedule, if the service is fee based, and where vaccines are procured. Health system mapping is important for identification of inefficiencies and the need for additional activities to achieve national immunization goals. The database is also critical for determining what regulations are needed.
- Countries that provide free vaccines to the private providers for administration should require those providers to report vaccine doses administered in a standard format using data recording tools and reporting processes from the NIP.
- Countries should establish clear reporting mechanisms between the private providers and the NIP to ensure that immunizations and related information (e.g. vaccine doses administered and disease and AEFI surveillance) are reported according to the same standards. The NIP should provide training and supervision on data recording and reporting to ensure appropriate and timely use by private providers leading to complete reporting.
- The private sector should be provided with adequate supplies of the national immunization/health cards recording tools, including home-based records, and health-education materials including checklists for systematic screening and vaccination job aides.

Provide adequate training and capacity building

- The NIP should increase communication and collaboration with private providers delivering vaccination services, tailored to the role and contribution of private providers to vaccine delivery. This includes information dissemination when new scientific findings are released, notification of changes to the national immunization schedule, private sector involvement during NIP trainings and consideration of designing specialized capacity building training programmes for health workers who provide vaccination at private facilities.
- All vaccinators in the private sector should undergo training on immunization. Initial training should be supplemented, ideally with yearly refresher courses followed by competency assessments. Key topics should include current schedules, new vaccines, storage, cold chain management, vaccine vial monitors, communication, advocacy, multiple injections, adverse events and notifiable disease reporting. If the private sector does not have the capacity to implement such training they should reach out to the NIP for support and guidance.

Facilitate accountability and performance oversight

- Countries are encouraged to engage the private sector through legislation regarding the development and implementation of immunization policies and laws. Policies and laws

should include surveillance, monitoring, reporting, and regulations pertaining to immunization services. Regulations can include vaccine schedules, licensing requirements, price controls, regulation of vaccines, regulation of private insurance, and fee waivers for specific populations.

- In the absence of specific legislation, countries are also encouraged to engage the private sector via contractual agreements or memoranda of understanding (MOUs). Contracts and MOUs should clearly state the role of both the government and the private sector and include supervision, surveillance, monitoring, training, and evaluation. They should explicitly note any payment that will be made to the private sector. Governments may need to increase capacity in development and negotiation of MOUs and contracts.
- Systems are needed to ensure adequate practices in all facilities delivering vaccines, including proper storage and handling, appropriate use of injections, screening for contraindications, proper recording and adherence to safety measures, and waste management and disposal. This may be managed by the health system through initial and/or periodic public health inspections, or by independent professional bodies.
- Countries should establish a system for the monitoring of quality standards by private providers. For countries that do not have infrastructure in place to implement regulations that are supported by monitoring and enforcement mechanisms, the NIP should provide documents to the private sector outlining guidance on regulations, enforcement, and compliance.
- There should be regulation and enforcement of adequate training of vaccine providers. This can be done through professional bodies or licensing legislation.
- Vaccines procured by private providers should be held to the same regulatory standards and oversight of the national regulatory authority (NRA) as those procured by the NIP. Regulatory requirements should not be waived for “free” or donated vaccines.
- NIPs should work through professional societies to develop and adopt standards of practice. NIPs should provide feedback to private providers on their performance relative to quality of services delivered
- Enforcement of the above recommendations can be achieved through a variety of mechanisms, but is challenging in resource-constrained settings. Professional self-regulation and third-party accreditation processes can relieve much of the regulatory burden from the government.

6. References

1. World Health Organization. Global Vaccine Action Plan. *Vaccine*. 2011;1–147.
2. Global Routine Immunization Strategies and Practices (GRISP): a companion document to the Global Vaccine Action Plan (GVAP). WHO, 2016. http://apps.who.int/iris/bitstream/10665/204500/1/9789241510103_eng.pdf?ua=1
3. Meeting of the Strategic Advisory Group of Experts on Immunization, April 2016 - conclusions and recommendations. *Weekly Epidemiological Record* 2016;21:266-284.
4. Levin A, Kaddar M. Role of the private sector in the provision of immunization services in low- and middle-income countries. *Health Policy Plan*. 2011;26(SUPPL. 1):4–12.
5. Mitrovich R, Marti M, Watkins M, Duclos P. A Literature Review of Immunization Service Delivery by the Private Sector in Low, Middle, and High-Income Countries. *Health Policy Plan*. Submitted for publication.
6. Lahariya C. Vaccine Epidemiology: A review. *J Fam Med Prim Care*. 2016;5(1):7–15.
7. Mills A, Brugha R, Hanson K, McPake B. What can be done about the private health sector in low-income countries? *Bull World Health Organ*. 2002;80(4):325–30.
8. Organisation for Economic Co-operation and Development. *A System of Health Accounts*. Paris. 2011;525.
9. United Nations Commission on Life-Saving Commodities Technical Reference Team on Private Sector Engagement. Private Sector Engagement: A Guidance Document for Supply Chains in the Modern Context. *Life-Saving Commodity Pract Netw* [Internet]. 2014; Available from: <http://www.lifesavingcommodities.org/private-sector-engagement-a-guidance-document-for-supply-chain-in-the-modern-context/>
10. Lydon P, Raubenheimer T, Arnot-krüger M, Zaffran M. Outsourcing vaccine logistics to the private sector : The evidence and lessons learned from the Western Cape Province in South-Africa. *Vaccine* [Internet]. Elsevier Ltd; 2015;33(29):3429–34. Available from: <http://dx.doi.org/10.1016/j.vaccine.2015.03.042>
11. Spring CP. Healthy partnerships : how governments can engage the private sector to improve health in Africa. [Internet]. World Bank; 2011 [cited 2016 Nov 5]. 152 p. Available from: <http://documents.worldbank.org/curated/en/323351468008450689/Healthy-partnerships-how-governments-can-engage-the-private-sector-to-improve-health-in-Africa>
12. Morgan R, Ensor T, Waters H. Performance of private sector health care: Implications for universal health coverage. *Lancet* [Internet]. Elsevier Ltd; 2016;388(10044):606–12. Available from: [http://dx.doi.org/10.1016/S0140-6736\(16\)00343-3](http://dx.doi.org/10.1016/S0140-6736(16)00343-3)
13. World Bank. 2008. *The business of health in Africa : partnering with the private sector to improve people's lives*. International Finance Corporation. Washington, DC: World Bank. <http://documents.worldbank.org/curated/en/878891468002994639/The-business-of-health-in-Africa-partnering-with-the-private-sector-to-improve-peoples-lives>
14. Olorunsaiye et al. Missed opportunities and barriers for vaccination: A descriptive analysis of private and public health facilities in four African countries. *Pan African Medical Journal* 2017. In press
15. Hagan, J et al. (2017) Knowledge, Attitudes, and Practices of Private Sector Routine Immunization Providers in Gujarat, India. Manuscript submitted for publication.
16. Metcalf CJE, Cohen C, Lessler J, McAnerney JM, Ntshoe GM, Puren A, et al. Implications of spatially heterogeneous vaccination coverage for the risk of congenital rubella syndrome in South Africa. *J R Soc Interface*. 2012;10(78).
17. Wallace, Aaron S., et al. "Experiences with provider and parental attitudes and practices regarding the administration of multiple injections during infant vaccination visits: lessons for vaccine introduction." *Vaccine* 32.41 (2014): 5301-5310.
18. World Health Organization. Global Vaccine Action Plan - Monitoring, Evaluation and Accountability. *Secr Annu Rep*. 2016.
19. Duclos P. National Immunization Technical Advisory Groups (NITAGs): Guidance for their establishment and strengthening. *Vaccine* [Internet]. World Health Organization; 2010;28(SUPPL. 1):A18–25. Available from: <http://dx.doi.org/10.1016/j.vaccine.2010.02.027>.
20. Thacker N, Choudhury P, Gargano LM, Weiss PS, Pazol K, Bahl S, et al. Comparison of attitudes about polio, polio immunization, and barriers to polio eradication between primary health center physicians and private pediatricians in India. *Int J Infect Dis*. International Society for Infectious Diseases; 2012;16(6):e417–23.
21. Horton R, Clark S. The perils and possibilities of the private health sector. *Lancet* [Internet]. Elsevier Ltd; 2016;388(10044):540–1. Available from: [http://dx.doi.org/10.1016/S0140-6736\(16\)30774-7](http://dx.doi.org/10.1016/S0140-6736(16)30774-7)
22. Johnson ML, Sterthous LM. *A Guide to Memorandum of Understanding Negotiation and Development* | ASPE [Internet]. 1982. Available from: <https://aspe.hhs.gov/basic-report/guide-memorandum-understanding-negotiation-and-development>
23. Zahner SJ. Memoranda of Understanding Between Medicaid MCOs and Public Health Departments [Internet]. *Managed Care Magazine Online*. 2001. Available from: <http://www.managedcaremag.com/archives/2001/9/memoranda-understanding-between-medicaid-mcos-and-public-health-departments>
24. USAID Deliver Project Task Order 1. *Emerging Trends in Supply Chain Management: Outsourcing Public Health Logistics in Developing Countries*. Arlington, Va; 2010.
25. United States Community Preventive Services Task Force. *Increasing Appropriate Vaccination: Provider Assessment and Feedback*. 2015.

Table 1. Proportion³ of private providers providing vaccination services and proportion of vaccinations provided by private providers, by World Health Organization (WHO) Region as reported in publications and expert interviews.

Data from recent review⁴ of papers since 2009 and from 2011 literature review⁵ of papers before 2009 (shaded)

Country (year data collected)	% Private providers providing vaccinations		% Vaccinations provided by private providers	Source of information	Comment
	For profit	Not-for profit			
WHO African Region					
Kenya (2010)	37	80		Olorunsaiye et al 2017	Service provision assessment (SPA) facility surveys
Tanzania (2014-15)	27	79		"	"
Senegal (2012-13)	30	79		"	"
Malawi (2013-14)	25	95		"	"
Kenya (2010)	34	80		Sood & Wagner, 2013	SPA; community, provider surveys
Nigeria, Abia State, 4 LGAs , urban, peri-urban (2011)			21	Oluoha et al, 2014	Monthly administrative data; 45% of facilities offering vaccine were private.
Uganda, Kampala (2010)			30	Babirye et al. 2014	30% respondents reported using for-profit providers
Ghana (2006)			40	Bass 2006	Mission hospitals. Traditional EPI estimates
Ethiopia (2006)			1 (0-3 across regions)	Ethiopia government	Survey 2006
Kenya, some north and northeast districts (2000)			45-60	Bass 2006	Traditional EPI vaccines
Mauritania (2003)			10	Ouedrigo 2003	Traditional EPI vaccines, Hep B, Hib
Morocco (1998)			5	Madrid report 1998	Hep B, Hib
Zimbabwe (1998)			0-3	Madrid report 1998	Hib

³ Percentages rounded to whole number

⁴ Mitrovich R, Marti M, Watkins M, Duclos P. A Literature Review of Immunization Service Delivery by the Private Sector in Low, Middle, and High-Income Countries. Draft.

⁵ Levin A, Kaddar M. Role of the private sector in the provision of immunization services in low- and middle-income countries. Health Policy Plan. 2011;26(SUPPL. 1):4-12.

WHO South-East Asia Region		UNICEF Coverage Survey 2009	Household survey;% partially/fully immunized in private sector
India total (2009)	9	"	"
India urban	21	"	"
India rural	6	"	"
India highest quintile	34	"	"
India range by state	1-28	"	1 (Sikkim)-28 (Delhi)
India,16 states.>90% India birth cohort.(2009-12)	5 (BCG)	Sharma et al. 2016	Estimate based on sales data. Weighted mean. Range 1 (Bihar)-17 (Punjab-Haryana)
	4 (Measles)	"	Range 1 (Assam)-19 (Kerala)
	2 (DTP3)	"	Range 1 (Orissa) - 7 (Kerala)
	4 (OPV)	"	Range 0.1 (W Bengal)-82 (Kerala)
	4 (Hib)	Sharma et al. 2015	OPV3> actual due to likelihood of >40PV doses/child
Bangladesh, Dhaka city ()	95	Uddin et al. 2012	
Bangladesh (2005)	1 (for-profit) 4 (not-for-profit)	Bass 2006	
Bangladesh (2000)	22 urban, 3 rural	Bass 2006	
Bangladesh, Dhaka (1999)	2	Levin 1999	
Bangladesh, Dhaka	62	Kahn 2004	NGOs
India	10	Peters 2002	
India 1995-6	17 in children, 36 in women	Howard and Roy 2004	National coverage survey
India, Madhya Pradesh	27 urban, 15 rural	Yoong 2007	
India, Chandigarh	66 (Hep B)	Puri 2007	
	45 (Hi)b	"	
	100 (typhoid)	"	
	100 (MMR)	"	
	100 (varicella)	"	
Sri Lanka 2007	15 national 34 (Columbo) 1 (Monaragala)	Agampodi and Amarasinghe 2007	0 in Anuradhapura Trincomalee, Matale
Thailand 1998	10 national, 33 urban	Madrid report, 1998	

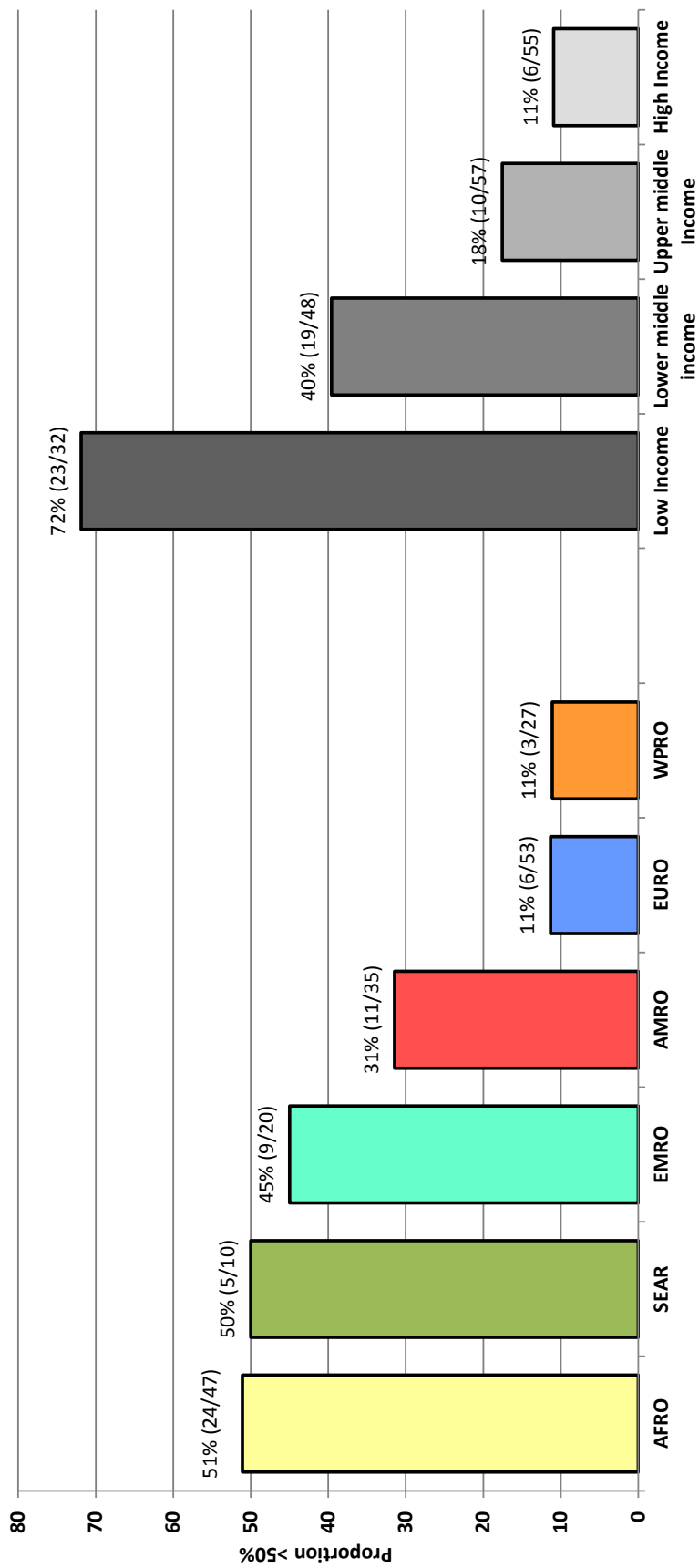
WHO Western-Pacific Region			
Philippines	10	L Suy 2016	Estimate from interview
Republic of Korea	60	Cho et al. 2010	
Cambodia	65 (provided at least 1 antigen)	Soeung et al. 2008	% of for-profit facilities offering specific antigens: 56 (HepB), 35 (tetanus), 10 (BCG), 4 (DTP), 4 (measles), 36 (rabies), 12 (typhoid), 10 (JE)
Cambodia	30-40	Bass 2006	
WHO Eastern Mediterranean Region			
Bahrain	<10	J Jawad, 2016	Estimate from interview
Lebanon	60 (for profit) 40 (not for profit)	A Rady 2016	Estimate from interview
Pakistan	97	Zaidi 2012	Zaidi A. Evaluation of GAVI Support to CSOs: Country Evaluation Report -2012
Pakistan (Karachi)	25	Zaidi 2012	
Pakistan, 2006	3	MOH Pakistan 2006	National coverage survey.4% for women vaccination
WHO Region of the Americas			
Caribbean	10-20	Irons & Dobbins 2011	
Mexico	5	J Santos 2016	Estimate provided in interview
Quebec, Canada	20	M Landry 2016	Estimate provided in interview
United States	61- exclusively in private 23-combination public/private	Groom et al. 2007	61% children vaccinated exclusively in private sector; 23% combination of public and private
Brazil, Sao Paulo state (2008)	1.3	De Soarez 2008	
Honduras	1.6	Epi Newsletter 1998	
Nicaragua	5	Epi Newsletter 1998	
Panama	15	Epi Newsletter 1998	
El Salvador	5-10	Epi Newsletter 1998	
Costa Rica	1-2	Epi Newsletter 1998	

WHO European Region			
Catalonia, Spain (2003-4)		31 (EPI series) 63 (varicella) 47 (PCV7) 52 (Hep B)	Borras et al, 2009 Telephone survey of parents of 3 yr-olds.
Germany		90	O Wichmann 2016 Estimate from interview
Greece		33	Pavlopoulou et al. 2013
Austria		90	O'Flanagan et al. 2012 Estimate reported in survey of vaccine program managers (children <3 yrs)
Belgium		20	"
Cyprus		57	"
Czech Republic		95	"
France		90	"
Greece		70	"
Hungary		<1	"
Ireland		100	"
Latvia		1	"
Luxemburg		100	"
Malta		10	"
Poland		5	"
Romania		10	"

Table 2. Summary of studies comparing vaccination coverage by private and public providers, as reported in literature

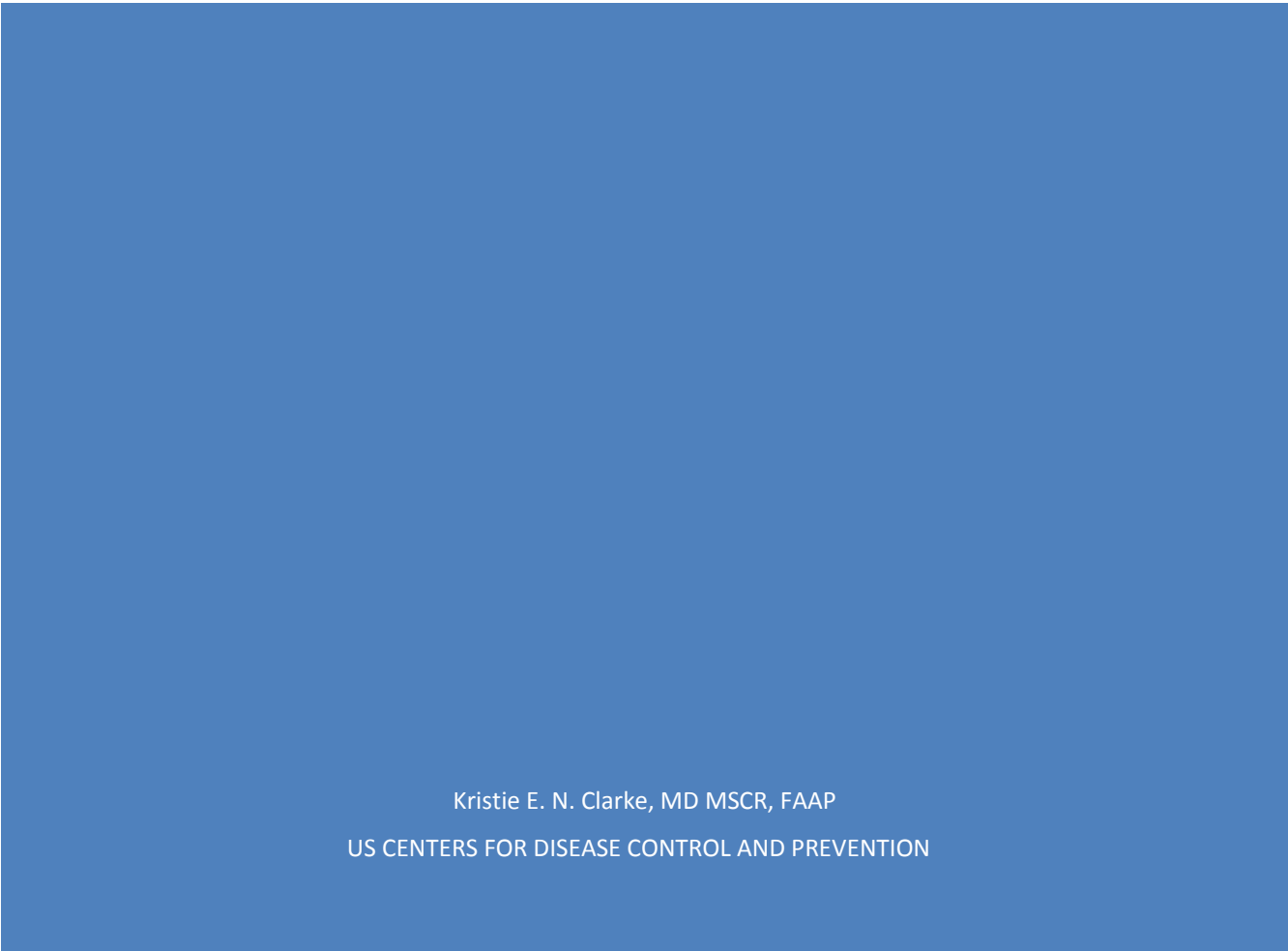
Country, Year, setting	Source	Vaccine	Study type	Coverage	Other finding
Kenya (2010)	Sood and Wagner 2013	No vaccination	Modelling from SPA and DHS surveys	Odds of not being vaccinated 4.8 times higher where facilities are for-profit compared to areas with no for-profit facilities.	
Sub-Saharan Africa	Wagner, 2014			BCG coverage for child born in private facility (45%), less than for child born in public facility (55%)	
Gabon, Libreville	Ategho et al. 2011	EPI antigens		Private for-profit coverage higher than public sector. Coverage of 3rd dose DPT, polio vaccine (90%), and measles (83%) at private clinics, 75% and 64% at public clinics.	
Philippines 2011, 142 government clinics, hospitals and private hospitals in regions with low Hep B-birth dose coverage.	Patel MK et al 2013	Timely (within 24 hrs of birth) Hep B- birth dose coverage	KAP	Private hospitals had lowest median timely HepB-birth dose coverage, 50% among private hospitals, 90% among government clinics, 87% among government hospitals ($p = 0.02$)	Private sector delivered 18% newborns. Private hospitals less likely to receive supervision (6–31%) than government facilities (53%) and to report vaccination data to EPI (36% vs. 96%–100%)
Vietnam	Murakami et al. 2008	Timely (within 72 hr of birth) Hep B- birth dose coverage		Hep B-BD (within 72 hrs of birth) coverage lowest (47%) in province with the highest % deliveries in private facilities	
Pakistan 2015 2 remote rural districts	Zaidi, 2015	BCG		In 1 district BCG coverage was 11 percentage points higher in contracted NGO clinics than in government clinics ($p < .01$), but not significantly different in other district. No difference in TT coverage between NGO and government facilities in either district.	
Catalonia Spain (2003–4). Survey of parents	Borras et al 2009	Basic series + booster		No difference in coverage (basic series+booster), 88% for both private and public	

Figure 1. Proportion of countries with >50% Private Expenditure on Health of Total Expenditure by WHO Region and Income Level (n=192)





REVIEW OF THE EPIDEMIOLOGY OF DIPHTHERIA – 2000-2016



Kristie E. N. Clarke, MD MSCR, FAAP
US CENTERS FOR DISEASE CONTROL AND PREVENTION

Background

Diphtheria was one of the leading causes of childhood death in the pre-vaccine era¹. However, after the diphtheria toxoid vaccine was invented in 1923, and subsequently was used on a large scale in the United States and other industrialized countries in the 1940s-1950s, incidence in these nations quickly declined. There was a continued decline after the launch of the Expanded Programme on Immunization (EPI) in 1977 (Figure 1). As a result, physicians in many nations have never seen a case of diphtheria and may be unaware that there are approximately 5000 cases of diphtheria reported worldwide each year².

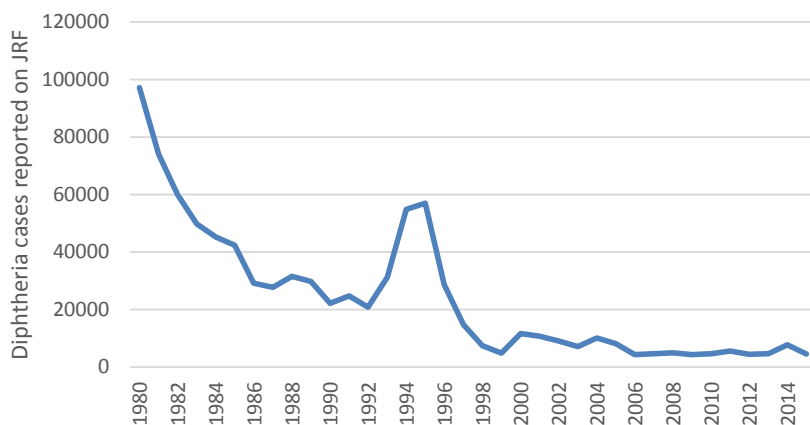


Figure 1- Reported cases of diphtheria worldwide- 1980 -2015

Diphtheria surged into the spotlight with a spike in incidence in the 1990s (Figure 1), representing a widespread epidemic in the Russian Federation and the former Soviet Republics, which left in its wake over 157,000 cases and 5,000 deaths¹. Cases tended to be much older than those in other contexts, with 64-76% among those aged 15 years and older³. This outbreak

demonstrates the potential for severe outbreaks when a community has both a large population of non-immune adults and poor vaccination coverage among children. The outbreak began in major urban centers in Russia at the end of the 1980s, but it was not readily acknowledged or addressed, and spread to all 15 post-Soviet Republics by 1995⁴. Reasons for the outbreak were rooted in falling support for vaccination among both parents and health care providers in the 1980s, with over 50 diagnoses listed as contraindications to vaccination and up to 50% of children in some areas receiving the less immunogenic adult formulation Td instead of the recommended DTP due to concerns about complications^{5, 6}. The decision of the Soviet Union in 1986 to delay the booster dose at school entry (age 6) to age 9 was also found to increase risk of infection in this population of children^{7, 8}. While there were high attack rates among many age groups, the highest incidence and highest proportion of severe cases were among 40-49 year olds, who were young children when DTP was being introduced in the Soviet Union. Many were not immunized as children and were also not exposed to the disease as incidence subsequently declined³. Meanwhile, cases did occur among younger adults who had been immunized, but these tended to be milder due to immunologic memory. With the breakup of the Soviet Union, there were also environmental conditions favorable to an outbreak, including large population migrations, declining socio-economic conditions, and disruptions of vaccination supply chains and programs in the former Soviet republics^{4, 7}. Importantly, serologic and case control studies at the time showed high vaccine effectiveness, proving that failure to vaccinate was the problem rather than vaccine failure⁹. The recommended response included the mass immunization of the entire population with at least one age-appropriate dose of diphtheria-containing vaccine, with those showing the lowest levels of immunity (30-50 yo adults) receiving a full 3 dose series of Td⁵. While the epidemic peaked at over 39,000 cases in 1994³, the effects were long lasting. As late as 2001 these nations accounted for over 12% of the cases of diphtheria reported worldwide (in 2015 this figure was just 0.2%)².

Patterns of epidemiology are known to have changed over time due to introduction of vaccination as well as changing socioeconomic conditions in countries. In the pre-vaccine era, children were exposed early; by 15 years of age, 80% of children were immune to diphtheria from either overt or subclinical infection. There was some age shift in diphtheria cases prior to the vaccine era. In Poland, >70% of cases in the 1890s were in children under 5, shifting to only 43% by the 1930s. This pre-vaccine era age shift has been attributed to an increased standard of living, smaller families, less overcrowding, and improved hygiene conditions. However, prior to vaccine introduction at least 40% of cases were still in children under 5, and 70% were in children under 15 years of age⁴. While children were susceptible, ongoing circulation served to naturally boost the immunity of adults.

After the introduction of vaccine in a population where diphtheria is endemic, the epidemiologic patterns have been described as following a two-stage process. In the first stage, the disease shifts to a greater proportion of cases in schoolchildren than described in the pre-vaccine era. In the second stage, cases are seen primarily in adolescents and young adults over age 15. In the aftermath of the 1990s outbreak, it was generally thought that in developing countries the pool of immunized individuals was still small enough that immunity would be maintained among adults by natural circulation. In developing countries in warm climates, cutaneous diphtheria, which serves to boost immunity without the symptoms or risks of classic diphtheria¹⁰, was an element of this continuing circulation. Cutaneous diphtheria does not meet the WHO case definition¹¹, so it is not reported as diphtheria on the JRF. It is also similar in appearance to, and may co-exist with, other cutaneous infections¹⁰ and is frequently not diagnosed. As a result, patterns of cutaneous disease among populations over time are not known or tracked.

In areas where diphtheria has been well controlled, immunity is known to wane in late childhood or adolescence depending on the schedule of immunization⁸. In many industrialized nations there are known gaps in immunity among the adult population, particularly those that were not exposed to the disease in their environment as children. The precise ages of adults most at risk varies by the country and timeline on which immunization for diphtheria was introduced⁴. In some countries, the immunity gap has been shown to be larger among women as compared to men; this had been attributed to booster vaccines received upon entry into military service or greater incidence of injury requiring tetanus vaccination^{7, 8, 12}. One of the lessons from the 1990s outbreak is that while a large group of susceptible adults does signal a potential for an outbreak, this is much less likely if the immunization coverage among children is strong. In the 1990s, there were many cases of imported cases of diphtheria to nearby countries such as Poland and Finland. However since these countries had maintained childhood immunization coverage of over 95%, there was no secondary transmission or local outbreaks as a result of these imported cases⁵. It is worth noting that marginalized or difficult to access populations in industrialized countries may still be at risk. In the US, toxigenic diphtheria had not been found to be circulating in national surveillance data, however on a Native American reservation in 1996 a strain was detected that was closely related to a strain seen in the same area in the 1970s, signaling likely continued undetected transmission⁷. Outbreaks in the 1980s were seen in the US and Europe among socioeconomically disadvantaged groups living in crowded conditions, primarily those with comorbid substance abuse⁴. While booster doses have been implemented in many countries and have the potential to address the known gaps, these have been difficult to monitor⁶. Despite the low compliance with the booster doses, the US Advisory Committee on Immunization Practices (ACIP) has continued to recommend decennial boosters despite controversy, in part due to the need to bolster diphtheria immunity among adults of all ages¹³. Another option to reach adults is to replace boosters of TT (such as after injury) with Td, although this can be slow to take effect. In 1991, the ACIP recommended adult vaccination with Td rather than TT be given at every opportunity due to increased

protection with only a marginal price difference; however, as late as 2000, 20% of adults were still receiving TT boosters⁷. Over time demand continued to drop and TT has not been available from manufacturers in the US since 2015.

With the exception of the universally recommended 3 dose primary series in infancy, the current WHO recommendation on diphtheria vaccine depends on the epidemiologic pattern of disease in each country. The first priority is attainment of 90% coverage for the primary series, with subsequent consideration of doses at the end of the second year of life and possibly additional doses at school entry and school leaving. Booster doses are especially recommended for industrialized countries which need to compensate for the loss of natural boosting from the environment. Those living in non-endemic or low endemic areas may require additional boosters at 10 year intervals¹⁰. There has recently been a call to reconsider these recommendations, with authors in some endemic countries noting a resurgence of the disease or a shift to older populations^{14, 15}, as well as anecdotal reports in the public health community of an age shift in developing countries that may be similar to that seen in previous years in industrialized countries. Therefore, this review gathered available case-based data regarding age distribution and vaccination status of infected persons. These data were analyzed in the context of available aggregate surveillance and coverage data in an attempt to shed light on the epidemiological patterns of diphtheria after the year 2000 and offer an evidence base for future recommendations.

Methods

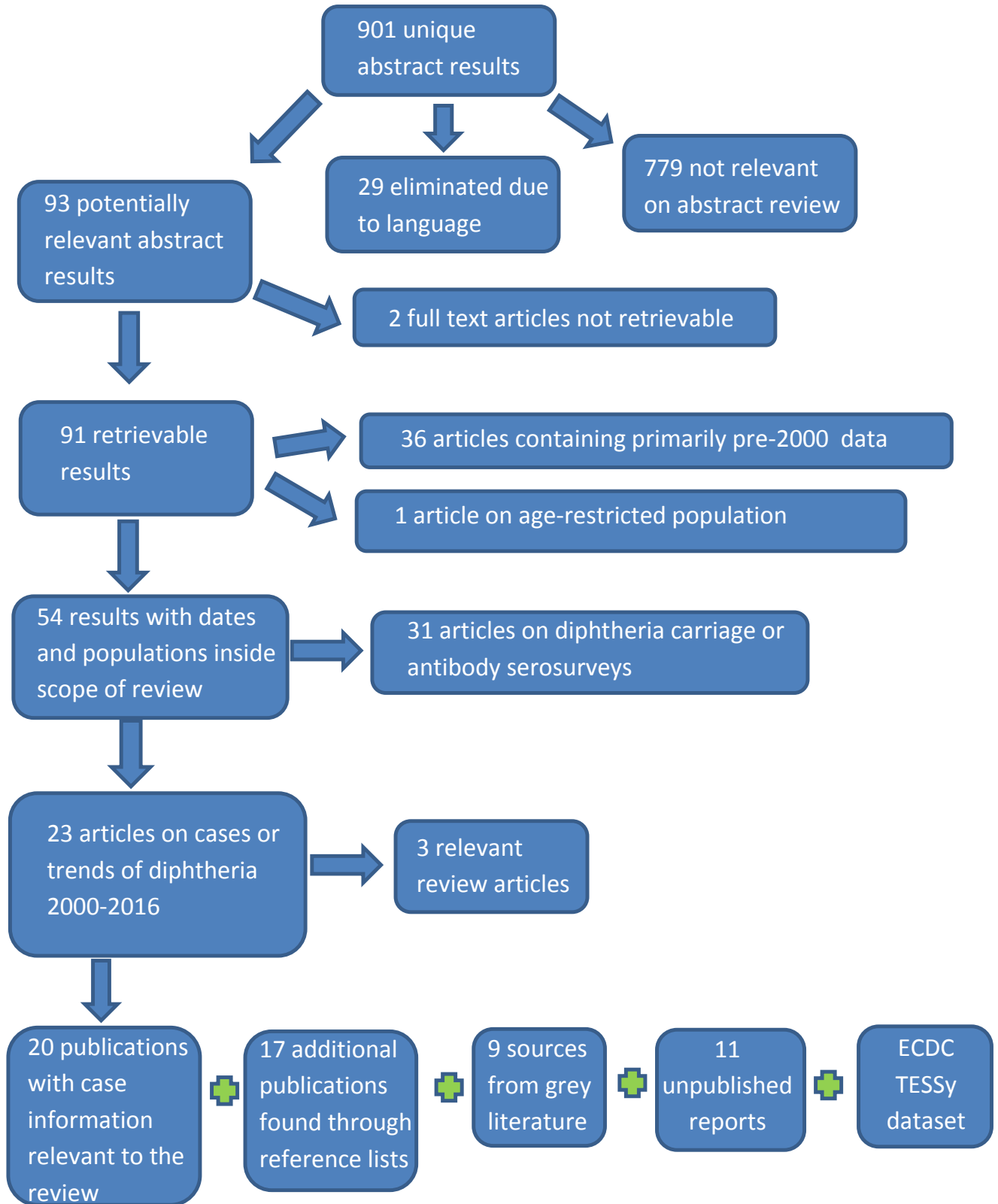
First, JRF data were examined for general epidemiologic trends of incidence over time and across regions. Recent patterns in immunization coverage and incidence were examined more in depth for the 10 countries reporting the most cases from 2010-2015. To contextualize the discussion of immunization recommendations, available databases and other information on national immunization schedules were compiled.

Next, since there is no repository of data on the age or vaccination status of cases of diphtheria, one was created using any accessible published or grey literature. An initial search was run on Medline and Embase with the assistance of a library sciences professional using the search terms diphtheria AND outbreak, cluster, OR epidemic. Once results were reviewed, a secondary search was performed to widen the scope of results on the Medline, Embase, Global Health, CINAHL, Cochrane Library, LILACS, and Scopus databases. See Appendix A for full search terms. The two searches returned 901 unique abstracts. Each abstract was reviewed by 2 members of the literature review team; any discrepancies in classifications were discussed until consensus was reached.

- *Inclusion criteria:* Publications containing age and/or vaccination status information on cases of respiratory diphtheria caused by *C. diphtheriae* between the years of 2000-2016
- *Exclusion criteria:* Publications not containing data on age or vaccination status variables, publications not available in English or Spanish in full text, those dealing exclusively with cutaneous diphtheria or diphtheria caused by another toxin-producing *Corynebacterium* species (e.g., *C. ulcerans*), publications discussing primarily cases diagnosed prior to 2000, and those reviewing outbreaks in age-restricted populations which are therefore not applicable to epidemiologic trends in the general population.

Three review articles were identified from the search^{1, 12, 16} and used to inform the background and analysis strategy in this report. Twenty publications with data on case age and/or vaccination status were identified^{14, 17-35}. Each was reviewed by at least two investigators, and relevant data were compiled in an Excel database.

Figure 2: Flow chart of literature review and sources for data used in analysis



During the review of the full-text articles, an additional 17 published manuscripts were identified through the reference lists^{15, 36-51}. A review of the grey literature resulted in 9 additional sources⁵²⁻⁶⁰, and communications with colleagues and partners in the field resulted in access to 11 unpublished reports containing relevant data⁶¹⁻⁷¹. In addition, diphtheria data from The European Surveillance System – TESSy, were provided by Spain, Latvia, Germany, Italy, Lithuania, the Netherlands, the United Kingdom, Finland, Sweden, France, Austria, and Belgium and released by the European Centre for Disease Prevention and Control⁷². See Figure 2 for the full flow diagram of the literature search and compilation of other sources. Due to the multiple data sources, care was taken that cases reported from the same country in the same year were not duplicates; if unclear, we conservatively excluded the case from the dataset.

The number of cases on the JRF for each country in the same year or set of years was included in the dataset for comparison. Since DTP3 coverage has been shown to be an important factor in the containment or spread of an outbreak, the average of the national WHO-UNICEF estimates of DTP3 coverage⁷³ for the previous 5 years were taken for each set of reported cases and included in the dataset. Countries with data included in the review were classified by the following categorical variables of interest (see Appendix B for a full list of variables and datasets created for this analysis):

- *Frequency of cases*: Higher case count countries (defined as reporting at least 10 cases in at least 3 years of JRF incidence data between 2000 and 2015) versus countries with sporadic cases
- *Vaccination schedule type*: Classified by age at last scheduled dose as 3 dose primary series in infancy only; Last booster dose at <6 years old; Last booster dose between 6 and 17 years of age, and Adult boosters (at least one dose of diphtheria-containing vaccine given at or after age 18).

The dataset was examined for patterns in both the age and vaccination status of reported cases. This analysis was complicated by three main factors. First, the age distribution analysis was complicated by the diverse ways in which age data were aggregated in sources. Our analysis used cutoffs at 5 years and 15 years for aggregation of age data since these were most frequently mentioned in the historical literature as benchmarks for the age shift in diphtheria incidence over time. In the 5 year analysis classifications were made using available cutoffs in the sources between 3 to 6 years of age; in the 15 year analysis classifications were made using cutoffs from 9 to 20 years of age depending on available data. Second, sources also aggregated vaccination status data differently. Cases with partial vaccination were grouped with fully vaccinated cases in several sources; these were conservatively designated as ‘partially vaccinated’ in the main dataset for aggregate analysis. Reports of cases with unknown vaccination status or partial vaccination were grouped with unvaccinated cases in other sources. These cases were conservatively designated as ‘unvaccinated’ in the main dataset for aggregate analysis. Finally, most reports or manuscripts did not have data that linked the age and vaccination status of cases or groups of cases; even if vaccination data and age data were available, it was not stated what percentage of cases in a specific age group were vaccinated, for example.

To analyze trends despite these limitations, 4 datasets were compiled for sensitivity analyses (see Appendix B):

- Dataset “5 Year” included all cases with clear age data of cases around the 5 year cut-off (± 1 year), excluding reports without age data.
- Dataset “15 Year” included those with clear case age data around this cutoff (± 1 year), excluding reports without age data.

- Dataset “Vaccine”, includes only those cases that were clearly categorized as unvaccinated, partially vaccinated, and completely vaccinated cases, as well as those with unknown vaccination status.
- Dataset “Age and Vaccination Status” included data from sources that reported the vaccination status of cases within each age group.

Incidence data were abstracted from the database of WHO Joint Reporting Form (JRF) results² and compared to the cases found in the literature over the same period as a measure of dataset completeness. Since it was being used as a metric for the dataset, the completeness of the JRF data itself was also examined.

Three key countries representing different regions and a range vaccination schedules which offered more complete and in-depth data are presented as case studies. For these countries, DTP3 coverage data from the WHO-UNICEF estimates were compared with incidence data from the JRF and the case datasets. If regional data on vaccination coverage and incidence were available, these were also compiled and factored into the analysis.

Distribution of cases by age and vaccination status were analyzed for all cases and across categories using basic descriptive methods. Sensitivity analyses looked for consistency of trends among cases with enhanced precision of data around each variable. Due to the heterogeneity of data, a valid meta-analysis could not be performed.

Results and Discussion

General epidemiologic trends, 2000-2015

After EPI implementation began in 1977 with diphtheria vaccine as one of the original six EPI antigens, the incidence of diphtheria worldwide dramatically decreased (Figure 1). We looked at reported diphtheria cases worldwide from JRF data as 5 year averages. Reported diphtheria cases declined from almost 10,000 cases per year during 2000-2004 to 5288 per year during 2005-2009. However, since 2009 annual reported cases have levelled off (Figure 2).

The South-East Asia region is the primary driver of global diphtheria incidence, especially since 2005 (Figure 3). Meanwhile, cases reported from the European and African regions have decreased.

Among countries with the top 10 case counts since 2000, India has the largest number of reported cases, with Indonesia and Nepal being the other main sources of diphtheria cases from the region (Figure 4). The Russian Federation and Ukraine were large contributors from 2000-2004 while the impact of a large outbreak during the 1990s was still attenuating; smaller numbers of cases were reported from other post-Soviet republics. A large number of cases was also reported from Nigeria in 2000-2004 but it does not figure prominently in the other time periods. However, this is likely an artifact of poor surveillance and reporting. Nigeria also has missing diphtheria data on the JRF for 11 years from 2000-2016, despite published cases in the literature for these years^{15, 43, 48}. Three other countries had large outbreaks during this time period: Madagascar and Papua New Guinea (with average DTP3 coverage of 72% and 61%,

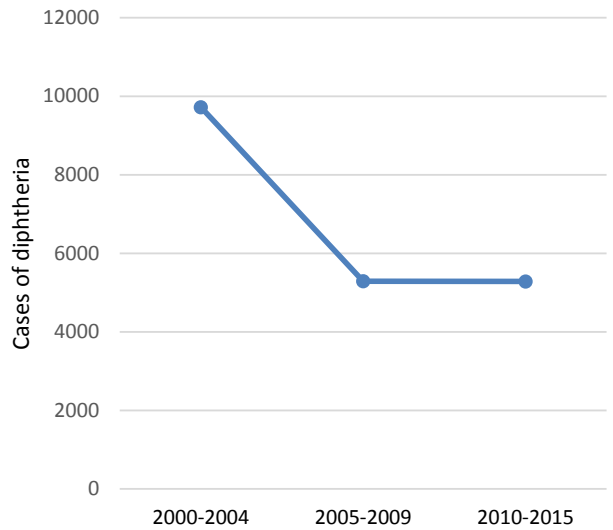


Figure 2: Reported cases of diphtheria per year worldwide by 5 year average

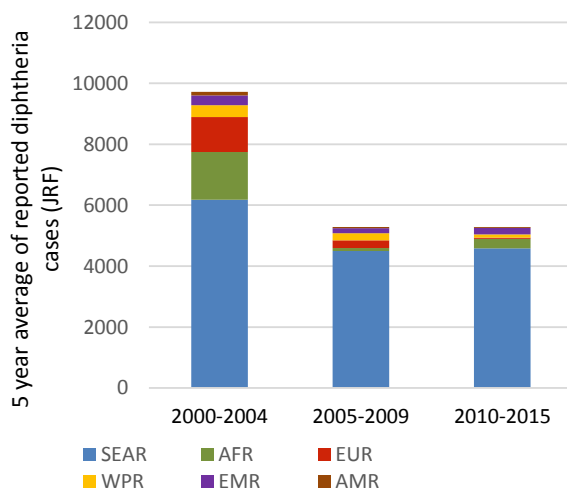


Figure 3: Cases of diphtheria by region by 5 year averages, 2000-2015

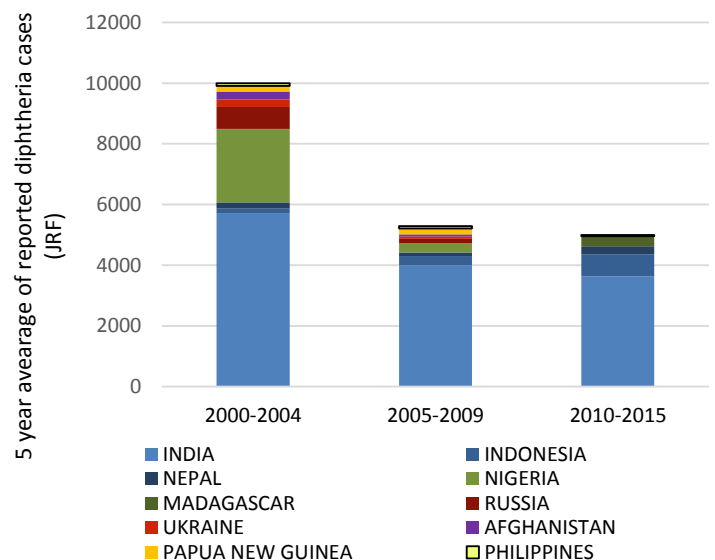


Figure 4: Reported diphtheria cases in the 10 highest case count countries by 5 year average - 2000-2015

respectively, prior to their outbreaks) and Nepal (90% DTP3 coverage). All three of these countries recommend 3 dose primary schedule without booster doses.

National vaccination schedules, 2016

Use of WHO recommended immunization schedules, after the 3 dose primary series, is dependent on country context. When the data from published manuscripts and grey literature were combined with data from online databases^{74, 75}, it was evident that countries recommend a wide variety of vaccination schedules. 49 countries (25%) administer only the 3 dose primary series, and 40 countries (21%) recommend at least one adult booster dose at or after age 18 (Figure 5).

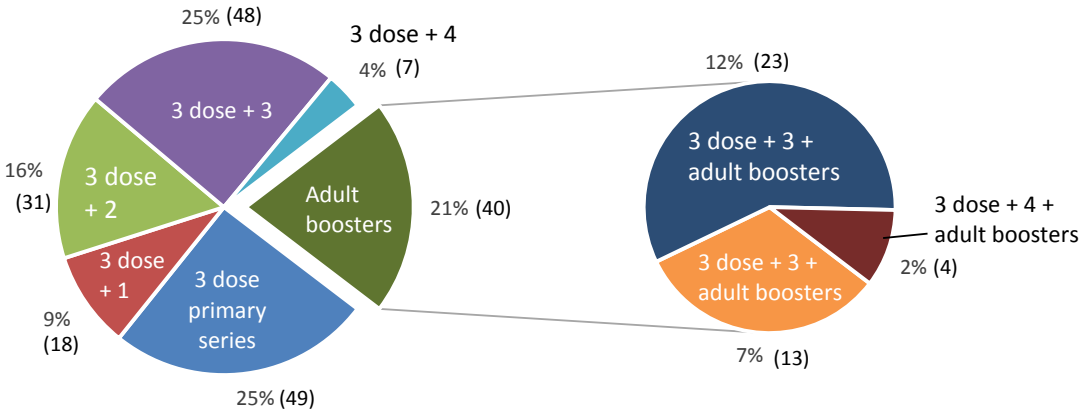


Figure 5: Percentage (number) of countries with each diphtheria vaccination schedule - 2016

The ages at which booster doses are administered are highly variable even among countries recommending the same number of booster doses (Table 1).

Although 25% of countries include only the primary schedule in their vaccination program, 6 of the 10 countries (60%) with highest reported numbers of diphtheria cases since 2011 recommend only the 3 dose primary series (Table 2). Of the 9 countries with a clear outbreak from 2005-2015 (defined as at least 2 years of reported case counts <10 followed by a year with >30 cases), 6 countries (67%) follow a 3 dose schedule, 2 follow a 3 +1 schedule, and 1 (Brazil) follows a 3 dose + 2 schedule. A historical record of changes to national schedules of diphtheria-containing vaccines is not available, so data reflect only current schedules as of 2016. Of note, 6 countries recommend 3 or 3 + 1

Vaccination Schedule	Median age (in years) at last scheduled childhood dose	Range of age at last scheduled childhood dose
3 dose primary series	N/A	N/A
3 dose + 1	5	1-15
3 dose + 2	6	<1-16
3 dose + 3	13	6-17
3 dose + 4	14	7-17
3 dose + 2 + adult boosters	12	5-15
3 dose + 3 + adult boosters	14	10-16
3 dose + 4 + adult boosters	16	14-17

Table 1: Median age at last childhood dose (and range) among countries recommending the same type of vaccination schedule

diphtheria vaccination schedules in which TT boosters are administered without a diphtheria vaccine component in later childhood or adolescence.

Country	Reported diphtheria cases (2011-2015)	Vaccination schedule	Age at last booster dose	Mean DTP3 coverage (2011-2015)
India	18350	3 dose + 2	5	84%
Indonesia	3203	3 dose + 4	8	82%
Madagascar	1633	3 dose	-	72%
Nepal	1440	3 dose	-	91%
Iran	513	3 dose + 2	6	99%
Lao PDR	344	3 dose	-	84%
Pakistan	321	3 dose	-	72%
Sudan	222	3 dose	-	93%
Myanmar	180	3 dose	-	79%
Thailand	157	3 dose + 2	4	99%

Table 2: Vaccination schedules and DTP3 coverage for the 10 countries reporting the most cases of diphtheria in 2011-2015

Availability of data on age and vaccination status of diphtheria cases, 2000-2016

Since only aggregate data are available from the JRF, we had to use other sources to compile the dataset for this review. After an extensive search for data on the age distribution and/or vaccination status of diphtheria cases from 2000-2016, a total of 10,919 cases of diphtheria from 33 countries were identified. By comparison, 106,750 diphtheria cases were reported from 97 countries on the JRF from 2000-2015. To better understand data availability and to contextualize our findings, we looked at data completeness in two ways- by country-year and by case numbers.

Over the period from 2000-2015, each country (with the exception of South Sudan) had the opportunity to submit 16 years of JRF data on diphtheria incidence to the WHO, for a maximum of 3092 potential country-years of data submitted. We assessed the completeness of the dataset created for this review as compared to the JRF incidence data. We also assessed the completeness of JRF diphtheria incidence data itself, since these data were being used as a metric of dataset completeness and represent the most thorough existing database for worldwide incidence. We classified each country-year into one of three categories: zero-reporting (the country included a report of zero diphtheria cases for that year), non-zero (for which a country reported a number of cases greater than zero), and missing (the country did not submit diphtheria incidence data for that year). Nonzero country-years were further separated into non-zero years with data captured in the review and non-zero years without data captured in the review. If at least one case reported from that country and year was included in the review dataset it was counted as a captured country-year, even if the number of cases in the review dataset did not equal the number of cases reported on the JRF. Overall, 63% of country-years were zero-reporting, 19% were non-zero and 18% were missing (Figure 6). Missing JRF diphtheria incidence data was not equally distributed among regions, with highest percentage of missing country-years in the African and Eastern Mediterranean regions. Therefore, even with the most complete data available we do not have a full picture of worldwide incidence.

Of the 600 country-years in which at least one case was reported, 85 (14%) were captured in the review dataset. The largest proportions of non-zero country-years with at least some data captured in the review dataset were in Europe (24%), South-East Asia (18%), and the Americas (12%). It is notable that 8,196 of the 10,919 cases in

the main review dataset (75%) were from India. However, this is proportionate to their overall contribution to case numbers worldwide (52-82% of globally reported cases each year from 2005 to 2015).

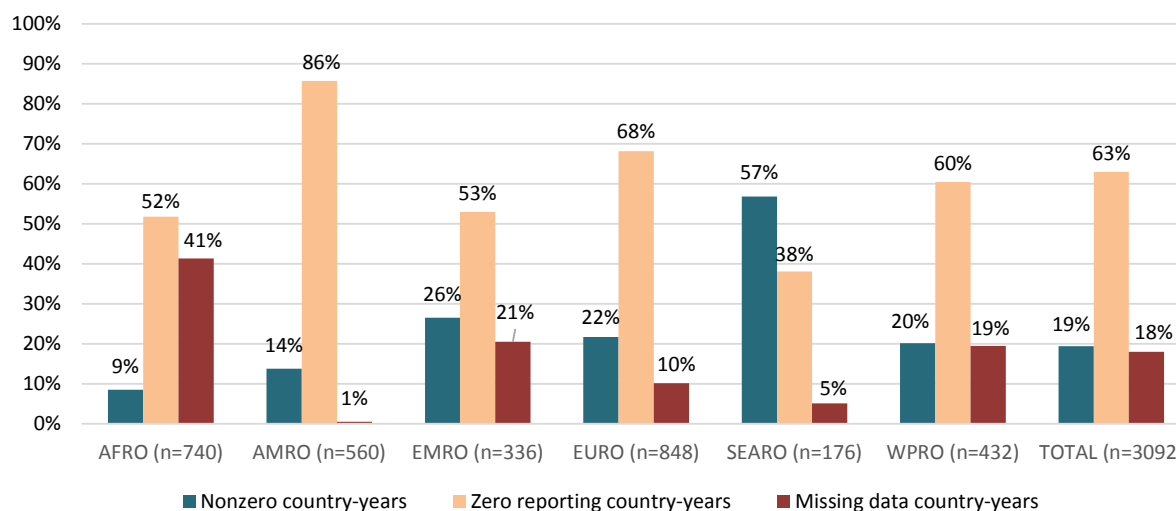


Figure 6: Summary of completeness of JRF diphtheria data by country-year – 2000-2015

There was much variability between regions in the completeness of cases included in the dataset. Data were most complete from the Americas and the Western Pacific region, with the number of cases captured in the review dataset totaling 34% and 20%, respectively, of the total incidence reported in those regions from 2000-2015 (Table 3). Because JRF data are aggregated, there is no way to ascertain how many of the same cases were captured by both datasets versus cases appearing in one dataset but not the other. This comparison also likely overestimates dataset completeness, since the dataset includes cases with 2016 data available, while the JRF data are only available up to 2015.

Region	Cases in review dataset	Cases reported from region, 2000-2015	Proportion of case number potentially captured in review
AFRO	133	10182	1%
AMRO	372	975	38%
EMRO	456	3785	12%
EURO	239	7244	3%
SEARO	8981	80866	11%
WPRO	738	3698	20%
TOTAL	10919	106750	10%

Table 3: Completeness of review dataset, by case numbers - 2000-2015

Finally, the years and countries with cases in the review dataset were cross-referenced with JRF data. In Figure 7, a subset of these data are shown for case counts under 150. Data points falling precisely on the diagonal line indicate a perfect concordance between the case number recorded in the review dataset and the number of diphtheria cases reported by the same country on the JRF during the same year. Data points under the line represent instances in which the country reported more cases on the JRF than were captured by the review; this is not surprising, as many manuscripts were regional

rather than national in scope. Points over the line represent instances in which the number of cases found by the review exceeded those reported by the country on the JRF; these are concerning and indicate poor reporting or surveillance. Overall, in 26 instances case data were included in the review from countries and years that had missing data or reported 0 cases for the corresponding year. In 7 additional cases, the number of cases found in the literature for a given country and year exceeded the nonzero number reported on the JRF.

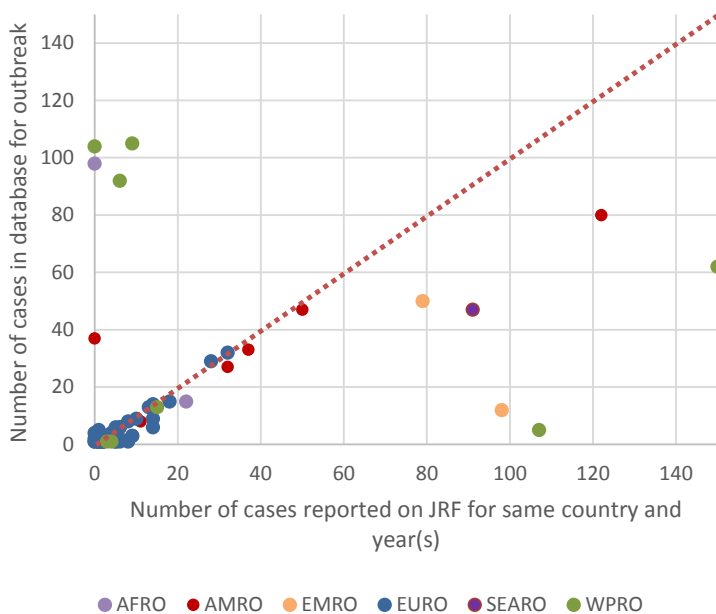


Figure 7: Concordance of cases captured in review and JRF reports

*for readability, depicts a subset of data with case counts under 150

years, 10,625 (97%) have data on an older age cut off near age 15 years, and 6,808 (62%) have at least some vaccination data available. In the “5 Year” dataset, there are 10,385 cases (95%) with data on an age cutoff at 5 (± 1) years; in the “15 Year” dataset, there are 5544 cases (51%) with data on an age cutoff at 15 (± 1) years. In the “Vaccine” dataset, there are 1360 cases (12%) with data that distinguishes clearly between fully, partially, and unvaccinated cases, as well as those of unknown vaccination status. Finally, in the “Age and Vaccination Status” dataset there are 3719 cases (34%) with some data on both age and vaccination status in endemic or high case count countries. See Appendix B for full details on the datasets used and sample size for each.

Numerous challenges in the quality and comparability of diphtheria case-based data across outbreaks were identified. While the overall case count in the review dataset is large, the sample size substantially decreases in some datasets demanding a higher level of clarity around specific variables.

Age distribution of diphtheria cases

In an overall analysis, 82% of cases worldwide were aged 5 years and older, while 42% were aged 15 years and over. These findings were consistent with those seen on sensitivity analyses of the “5 Year” and “15 Year” datasets.

Age distribution in high case count countries v. sporadic incidence countries

Similar age distributions are seen for the 5 year age cutoff in high case count countries and those with sporadic incidence in analysis of the main dataset, although on sensitivity analysis with the “5 Year” dataset, age distributions in sporadic incidence countries jump to 92% in the over 5 age group (See Appendix B for definitions of these variables and sample size of each group).

Overall, the most salient points from this portion of the analysis include the poor availability of case-based data for review and the lack of representativeness of these data on a global scale due to overrepresentation of some regions. The review of JRF data demonstrated the lack of completeness, and at times accuracy, of diphtheria data submitted to the WHO, highlighting regional differences in surveillance and reporting quality.

Quality of data on age and vaccination status of diphtheria cases, 2000-2016

Several datasets were created for sensitivity analyses due to the wide variety of categories used by authors to aggregate cases by age and/or vaccination status. The main review dataset includes 10,919 cases; 10,517 (96%) of these have some data on a younger age cut off near age 5

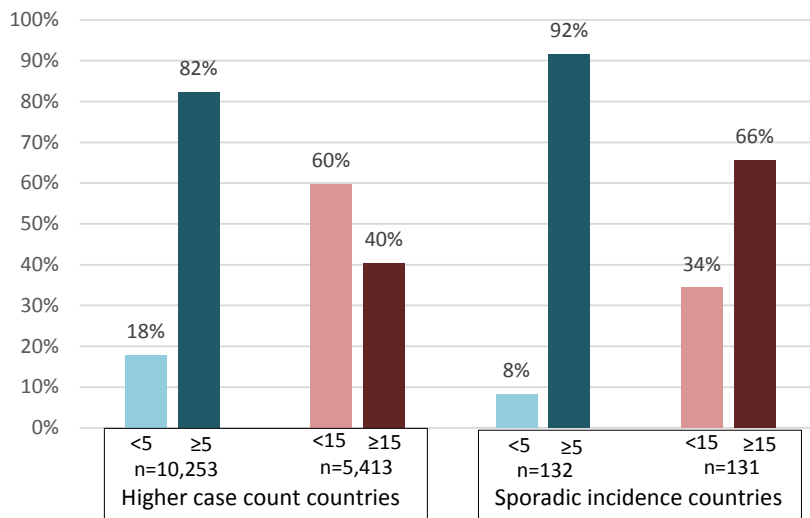


Figure 8: Sensitivity analysis of age distribution in higher case count versus sporadic incidence countries (using "5 Year" and "15 Year" datasets)

Age distributions are different across the 15 year age cutoff. In high case count countries, approximately 60% of cases are in those under 15, while in sporadic incidence countries the proportions were reversed- 66% of cases were in those 15 and older. This was consistent across sensitivity analyses (Figure 8).

In summary, while age distributions in both categories show the effects of vaccination, countries with higher case counts appear more likely to be in the first stage of the shift in age distribution post-vaccine introduction, in which the preponderance of cases occur in school-age children. By contrast, in countries with sporadic incidence the second stage of the shift in age distribution seems more common, with most cases in older adolescents and adults.

Age distribution by national vaccination schedule

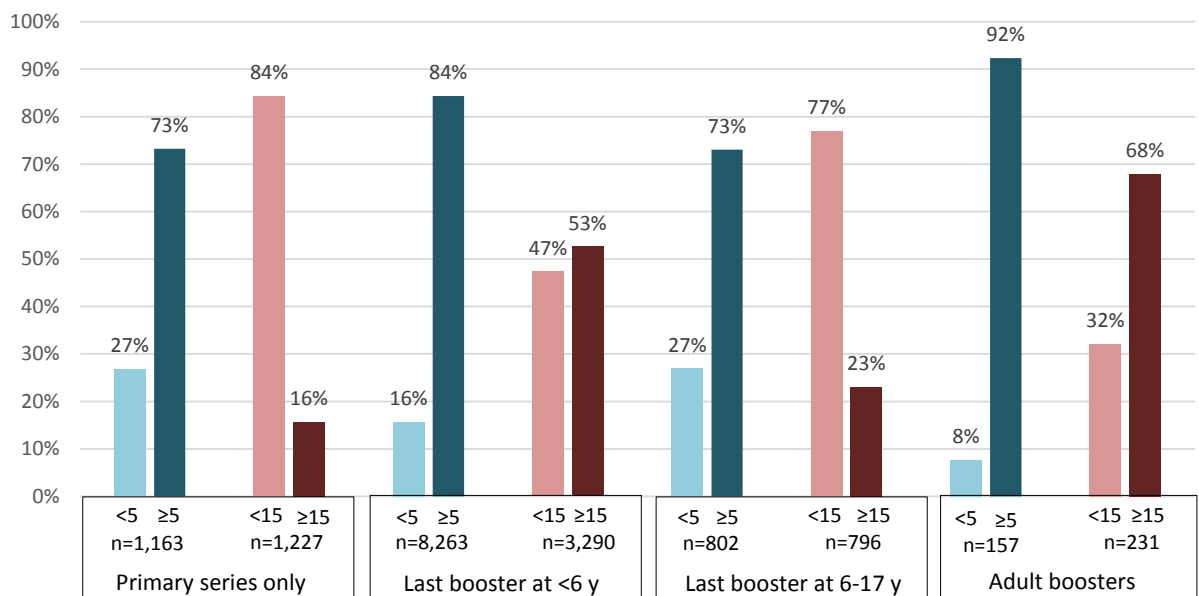


Figure 9: Sensitivity analysis of age distribution by vaccination schedule type (using "5 year" and "15 year" datasets)

Regardless of vaccination schedule, cases were predominantly (>70%) aged 5 years or older across sensitivity analyses. There was more variability of proportions across the 15 year age cutoff. There was

a predominance of cases among persons aged 15 and over only from countries offering adult boosters. In contrast, a larger proportion of cases occurred among persons under 15 years of age in countries offering just the primary series and those offering the last booster between 6-17 years of age. The age distribution of cases in countries offering the last booster before 6 years of age was more evenly split around the 15 year cutoff. However, this group was largely dominated by cases from India (75%) and might better represent the trends from one nation rather than countries using the vaccination schedule as a group. These cases showed a slight predominance (54%) of cases under 15 on analysis of the main dataset, which switched to a predominance of cases 15 and up (53%) on sensitivity analysis with the “15 Year” dataset (Figure 9).

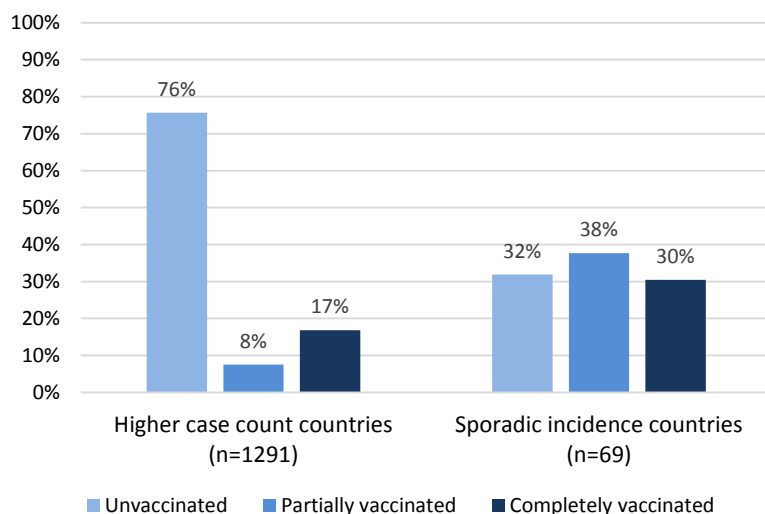
Overall, the first stage of the age shift (predominance of cases in school-age children) seems to apply to countries in the dataset recommending either the primary schedule or giving the last booster to school-age children. The group of countries giving the last dose prior to age 6 years (predominantly India) had a pattern in which case counts were similar above and below age 15 years; this could potentially suggest a transition between the first and second stage of the age shift, in which more cases are occurring in older adolescents and adults but they still do not represent the majority of cases.

Vaccination status of diphtheria cases

On analysis, 65% of cases were unvaccinated, 12% were partially vaccinated, and 23% were fully vaccinated. On sensitivity analysis with the “Vaccine” database, the proportion of unvaccinated cases rose to 73%, while there were lower proportions of cases that received vaccines. It is notable that different sources had different definitions (when stated) for “fully vaccinated” depending on the vaccination schedule of the country or preferences of the investigators. However, in general fully vaccinated can be considered as receiving at least all 3 doses of the primary series.

Vaccination status of cases in high case count countries versus sporadic incidence countries

In countries with high case counts, the majority of cases were unvaccinated in both analyses (65% in the main review dataset and 76% in the sensitivity analysis with the “Vaccine” dataset). In countries with sporadic incidence, about one third of cases each were unvaccinated, partially vaccinated, and



completely vaccinated on both the main and sensitivity analysis (Figure 10).

These findings may indicate that the main challenge in countries with high case counts is achieving adequate coverage with the primary series. In countries with sporadic incidence, the predominance of older cases taken together with the relatively even distribution of vaccination status indicate that waning immunity might be a bigger issue.

Figure 10: Sensitivity analysis of vaccination status of cases in higher case count versus sporadic incidence countries (using "Vaccine" dataset)

Vaccination status of cases in countries with different vaccination schedules

In countries with all vaccination schedules, $\geq 39\%$ of cases were unvaccinated on all analyses. This percentage was 70% or over for countries offering the primary series, 66%-88% for those offering a booster before 6 years of age (depending on dataset used), and 39%-58% for those

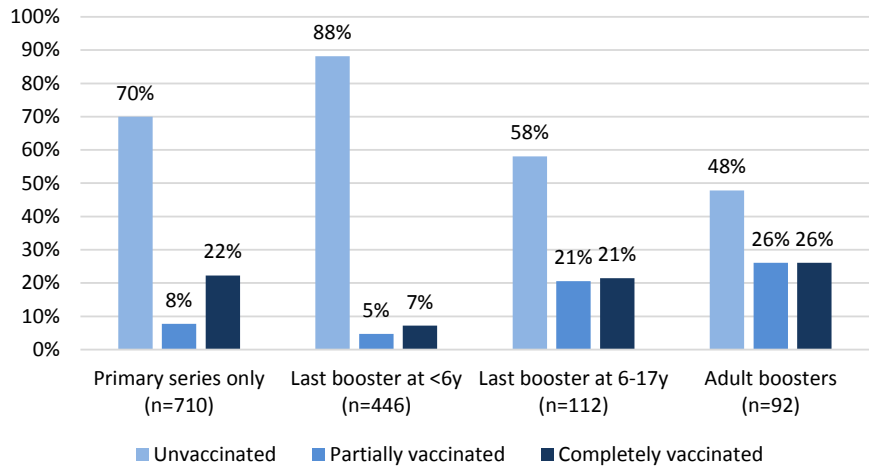


Figure 11: Sensitivity analysis of vaccination status of cases by vaccination schedule (using "Vaccine" dataset)

offering a booster after 6 years of age. Among cases in countries offering adult boosters in all analyses, 48% were unvaccinated, 26% were partially vaccinated and 26% were fully vaccinated (Figure 11).

Overall, countries offering the primary series or boosters only before the age of 6 had a higher proportion of unvaccinated cases as compared to those offering later boosters, including adult boosters. This might indicate that countries using vaccination schedules in which the last diphtheria-containing dose was administered at a younger age have not added doses because they are still striving to achieve optimal coverage with the current schedule.

Relationship between age distribution and vaccination coverage

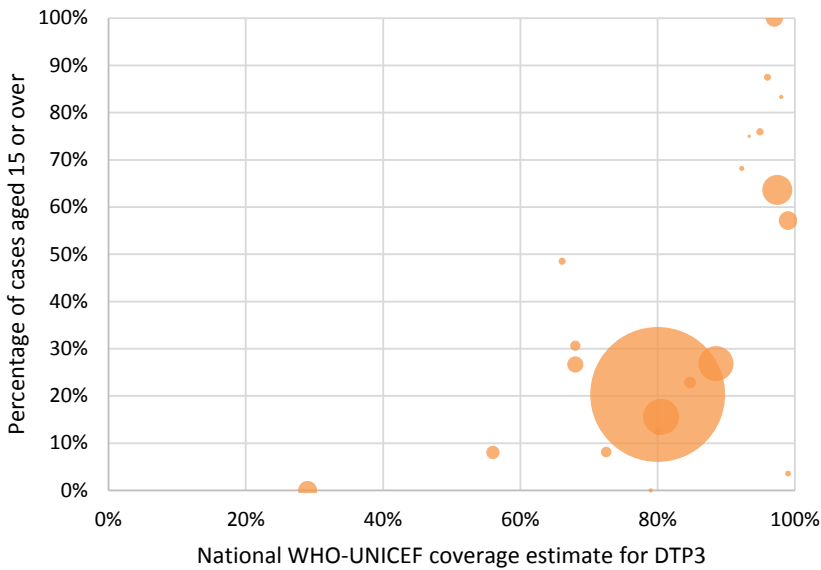


Figure 12: Percentage of diphtheria cases reviewed aged 15+ by national DTP3 coverage

Since vaccination coverage with the primary series has been highlighted as a factor influencing age distribution, this was specifically examined in these data. The total cases for each country were combined, and the average of the 5 years of DTP3 coverage (per WHO-UNICEF estimates) for the year(s) in question was taken. Countries with under 5 cases were excluded from this analysis. The percentage of cases aged 15 or over are plotted on the y axis, and DTP3 coverage on the x axis. Each dot represents a country, and its size is proportionate to the total number of cases reported from the country. In both the main dataset and

a sensitivity analysis run on the “15 year” dataset, there is a visible trend toward a higher percentage of cases aged 15 and over in countries with higher DTP3 coverage. In both analyses, countries with DTP3 coverage over 90% tend to have over half of their cases in people aged 15 or over (Figure 12).

Relationship between age distribution and vaccination status of individual cases

In the dataset “Age and vaccination status” there are 3719 cases for which data on both age and vaccination status are available. The age and vaccination status aggregation challenges mentioned previously for the entire dataset also apply to this subset of data. Data are included from Nigeria, Myanmar, the Philippines, India, Haiti, Indonesia, Latvia, and Brazil. The majority of cases in each age group were unvaccinated; the largest proportion of unvaccinated cases were seen in the 15 and up age group. About a third (30%) were completely vaccinated, with most of these cases being in individuals over the age of 5.

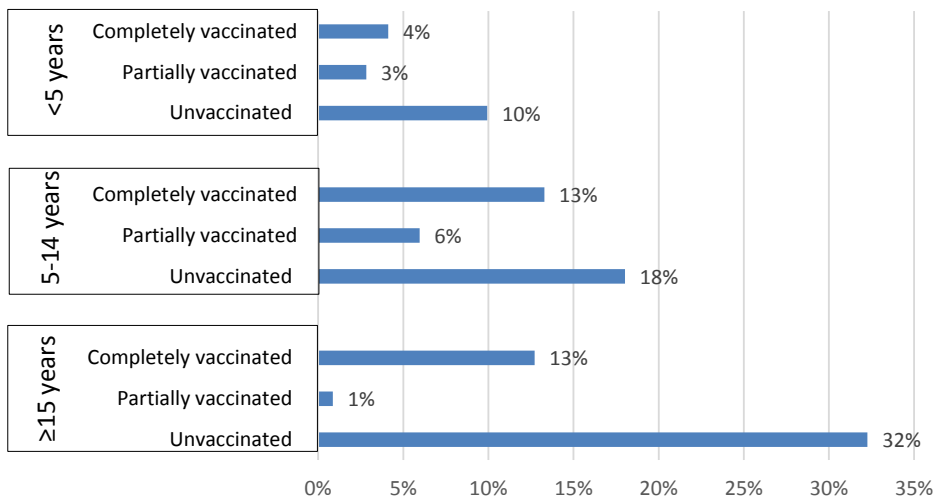


Figure 13: Distribution of age and vaccination status among all cases with vaccination status for each age group (n=3719)

Among countries in this dataset following the primary series only (Nigeria, Myanmar, and the Philippines), 69% of cases were unvaccinated. Among completely vaccinated cases (24%), the largest proportion were among those aged 5-14 years (Figure 13).

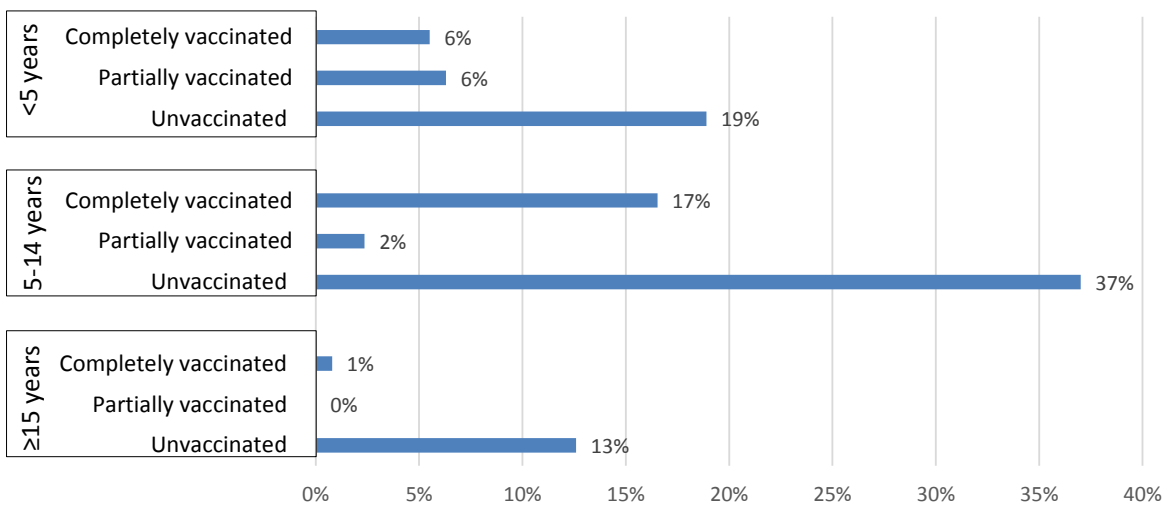


Figure 14: Distribution of age and vaccination status among cases in countries offering the primary series only (n=127)

These data indicate that the lack of vaccination with the primary series tends to be the principal risk factor for infection, yet also support evidence that immunity does wane and booster doses may be relevant. Among countries using the primary vaccination schedule, the fact that the largest proportion of completely vaccinated cases is among school-age children is not surprising, as immunity may wane at this age if the last dose of vaccine is given in the first year of life⁸. It is also an age when children are at high risk of transmission of infectious disease in a school setting. Of note, other vaccination schedule groups were dominated by cases from a single nation, and will be discussed below in the case studies.

Case studies

India

India has followed a 3 + 2 dose schedule since EPI was launched in the country in 1978, with the boosters given at 1.5 and 5 years of age⁷⁶. Despite great progress in both vaccination coverage and reduction of incidence in

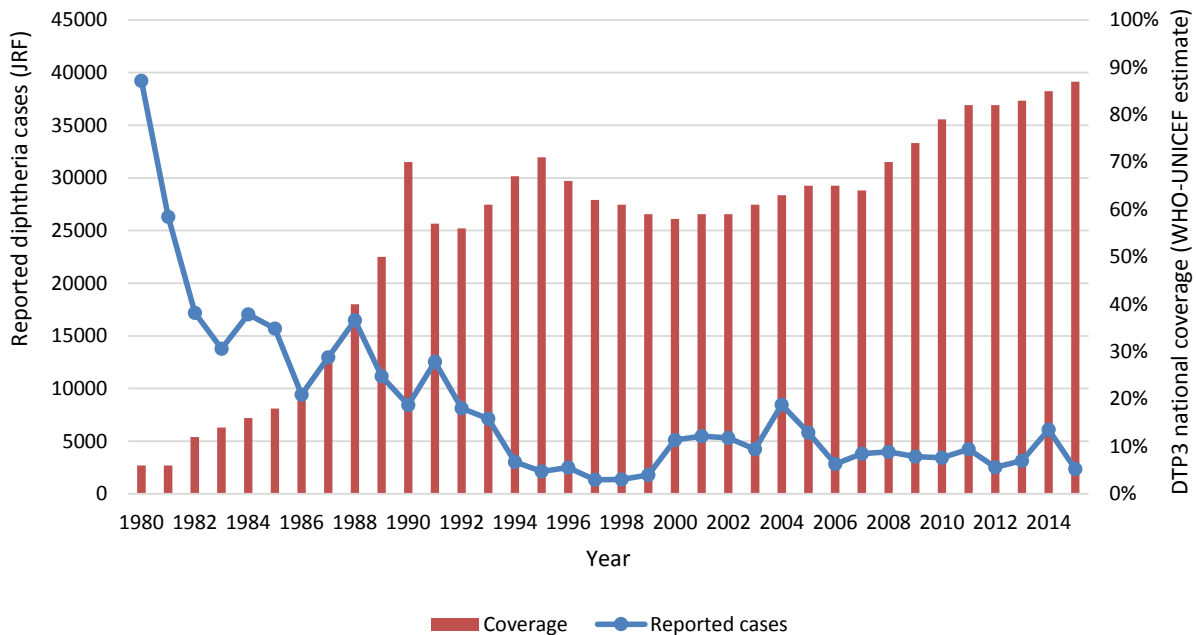


Figure 15: Diphtheria Incidence and DPT3 Coverage Trends - India, 1980-2015

recent years (Figure 14), India consistently reports the greatest number of cases, making this a key country to examine. In recent years, several articles and letters have been published noting the persistence or perceived resurgence of diphtheria in India and querying whether improved surveillance and additional booster doses should be recommended^{14, 37, 40, 42, 77}. Fortunately, India has recently implemented a case-based surveillance system, and data from this system were included in this review⁷¹. To better understand coverage trends in India and subnationally, survey data were also examined from various sources⁷⁸⁻⁸⁶.

The review dataset captured 8196 cases from India ranging from 1997-2016 from 12 sources, compared to 70,361 cases reported on the JRF from 2000-2015. Among those cases, 67% were unvaccinated but a substantial proportion (26%) were completely vaccinated. While most cases analyzed in India were over 5 years of age, percentages of cases below and above 15 years of age were 51% and 48%, respectively. When a sensitivity analysis was conducted using the “15 Year” dataset, 55% of cases were 15 or older as compared to 45% under 15 years of age. However, the question remains: are these cases susceptible because they were unvaccinated or due to waning immunity?

We approached this question in two ways; first, the incidence and coverage trends were assessed. Out of the population analyzed above, cases 15 years of age would have been born in 1982- 1998, a period when DTP3 coverage was still ramping up (Figure 14). Therefore it is likely many of these cases in adolescents and adults are in unvaccinated individuals. Because diphtheria incidence dropped sharply in the early 1980s, it is also likely that, even if vaccinated, immunity in this population may have waned due to lower exposure to disease in the community compared to previous generations. Secondly, a study was examined which showed linked vaccination and age data in a large population (n=2925 cases) in India from 2008-2012³⁵. In this study, 41% of cases were reported to be completely vaccinated. Out of those unvaccinated and partially vaccinated (reported in aggregate), most cases were aged 15 years and older, while cases among completely vaccinated cases were

predominantly amongst those 5-14 years old and those aged over 15 (Figure 16).

Therefore, the data available show both a cohort effect of lower primary series coverage (DTP3 coverage was between 60%-70% when 15 year olds in this group were infants) and also a high percentage of cases among older vaccinated individuals which could indicate waning immunity.

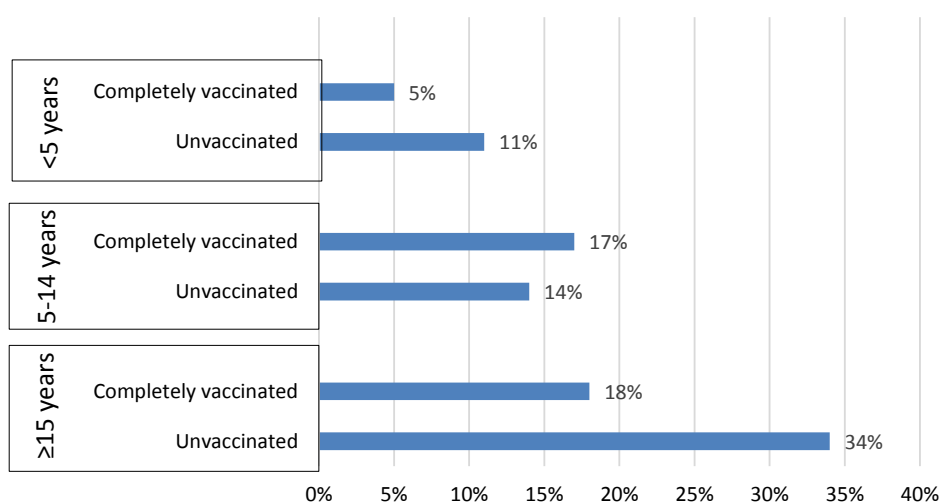


Figure 16: Distribution of age and vaccination status among cases in Andhra Pradesh, India – 2008-2012 (n=2925)

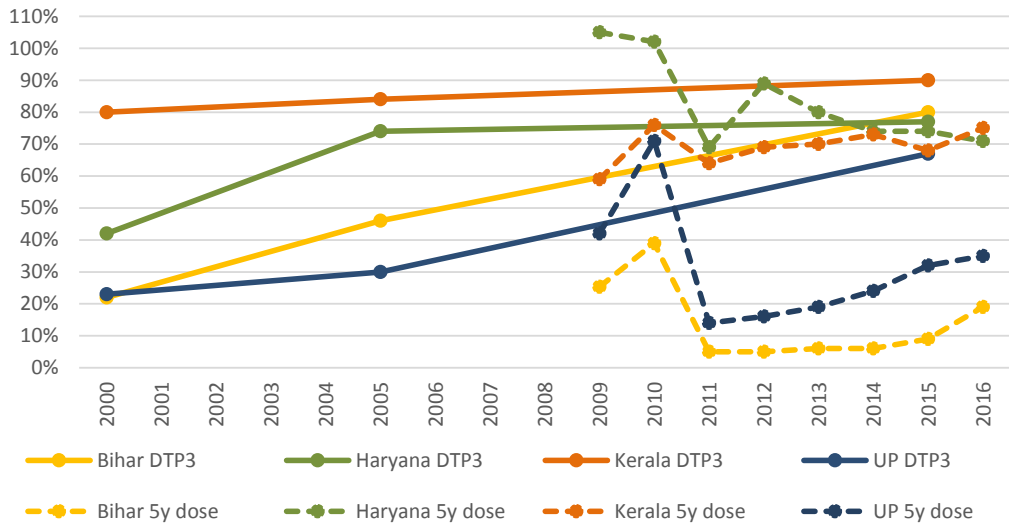
The 2016 surveillance data, which comes from the states of Bihar, Haryana, Kerala, and

Uttar Pradesh (UP), shows the importance of examining subnational surveillance data and coverage. The age distribution of cases for these states is very different, with Bihar having the highest proportion of cases under 5, Kerala having the highest proportion of cases over 10, and Haryana and UP showing the highest proportion of cases between 5 and 10 years of age (Table 4). Survey data demonstrate that the coverage for both DTP3 and the fifth dose at 5 years of age is also highly variable among regions (Figure 17).

State	Total cases	Under 5	5-10 years	Over 10
Bihar	71	41%	34%	25%
Haryana	59	27%	53%	20%
Kerala	556	8%	18%	74%
Uttar Pradesh	844	25%	53%	22%
Total	1530	20%	39%	41%

Table 4: Age distribution of cases in states of India with case-based surveillance, 2016

Overall, the large proportion of cases under 5 in Bihar is probably explained by the very recent ramp up in DTP3 coverage along with the still very low coverage with the 5 year booster dose, yet it is surprising that UP shows a



a different age distribution, since vaccination coverage patterns are similar. In Kerala, the consistently higher coverage with both DTP3 and the 5 year booster explain the predominance of cases in the oldest age group. While the vaccination coverage in Haryana is substantially higher than in the two other states, DTP3 coverage is still approximately 10 absolute percentage

Figure 17: Trends in DTP3 and 5yr booster coverage in States with case-based diphtheria surveillance - India, 2000-2015

points lower compared to Kerala, which could explain the differences in age distribution.

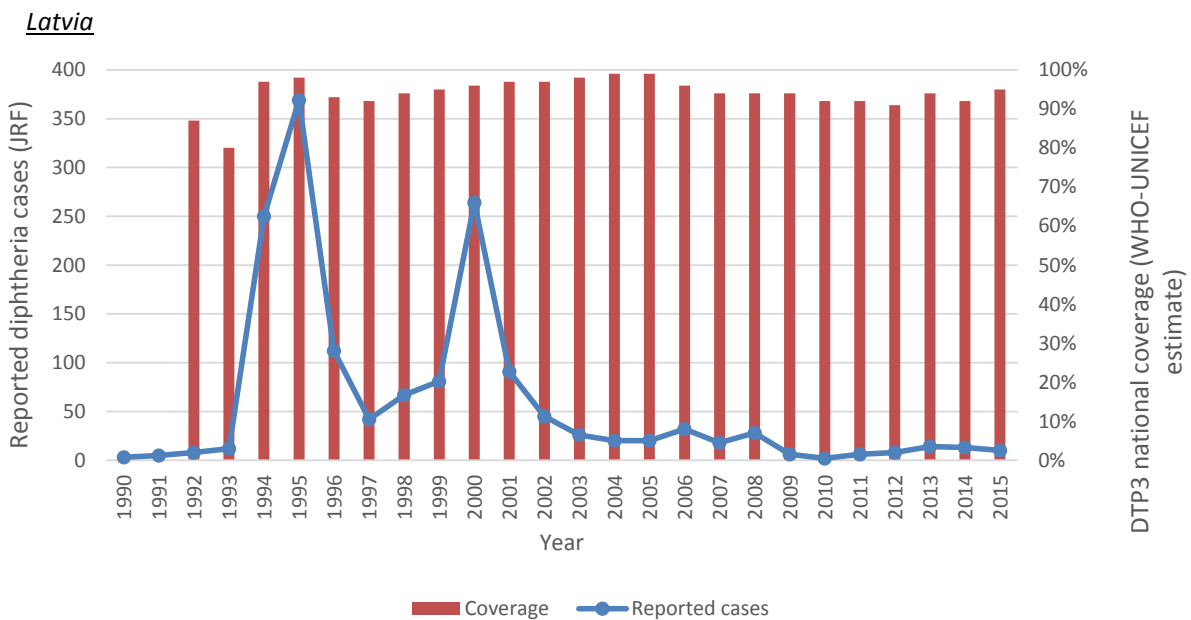


Figure 18: Diphtheria Incidence and DTP3 Coverage Trends - Latvia, 1990-2015

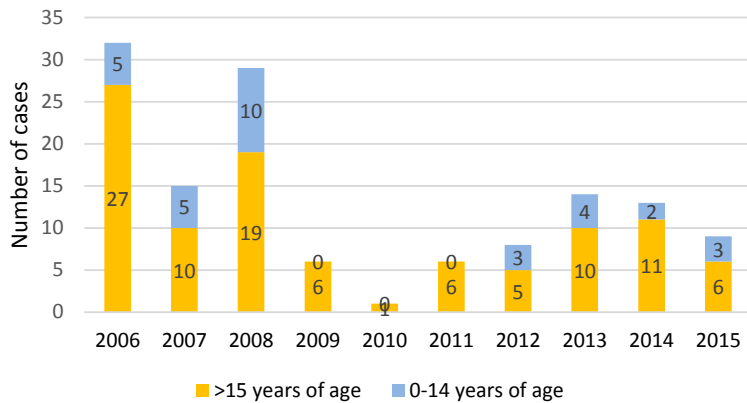


Figure 19: Age distribution of cases in Latvia, 2006-2015 (n=98)

vaccination as infants and not exposed to the disease in their environment due to rapidly declining incidence⁸⁷. This is consistent with data available from 2006-2015, which shows that while diphtheria incidence has declined over this period, even in recent years the majority of cases are in those 15 years of age or older (Figure 19). When the age distribution of these cases is further broken down, many of these cases are in the same cohort shown to be most at risk in the 1994-2014 study, now aged 60 and above (Figure 20). Both age and vaccination status data are available for a subset of cases from Latvia in 2011-2015 (Figure 21). This shows quite a different distribution from other case studies, with most cases in unvaccinated adults; this is also consistent with the 1994-2014 data.

DTP3 coverage has historically been high in Latvia, with a brief dip in the early 1990s followed by the well-documented outbreak in that country and several other post-Soviet republics (Figure 18). Routine adult boosters have been recommended since 1994. From 1994 to 2014, 43% of cases were in individuals 40 years of age or older, who were born near the time of the introduction of DTP vaccine in the former Soviet Union. Many in this group were both missed by

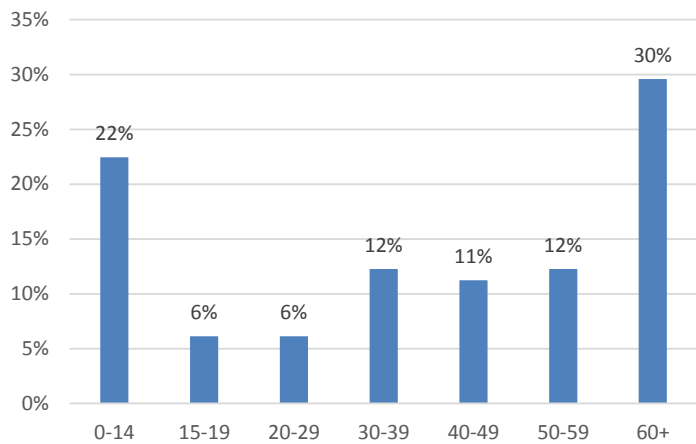


Figure 20: Age distribution of cases in Latvia by year, 2006-2015 (n=98)

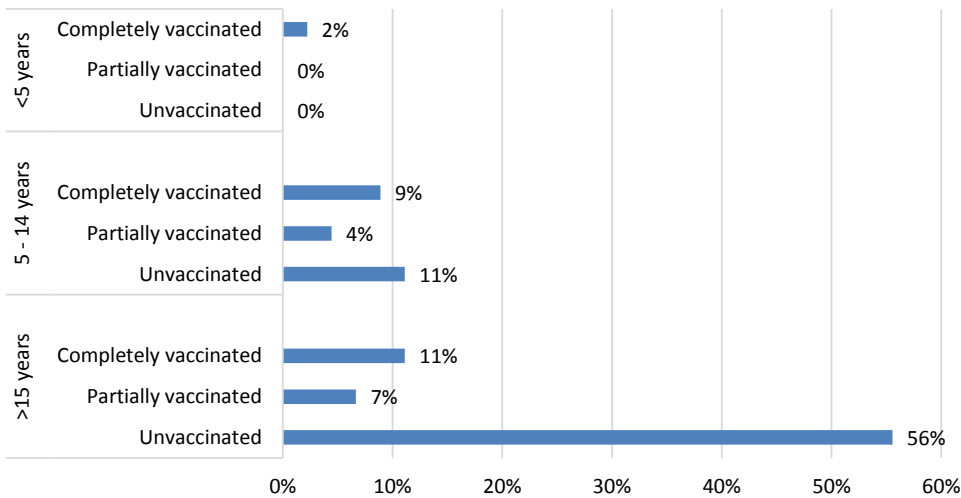


Figure 21: Vaccination status and age of cases in Latvia, 2011-2015 (n=45)

Philippines

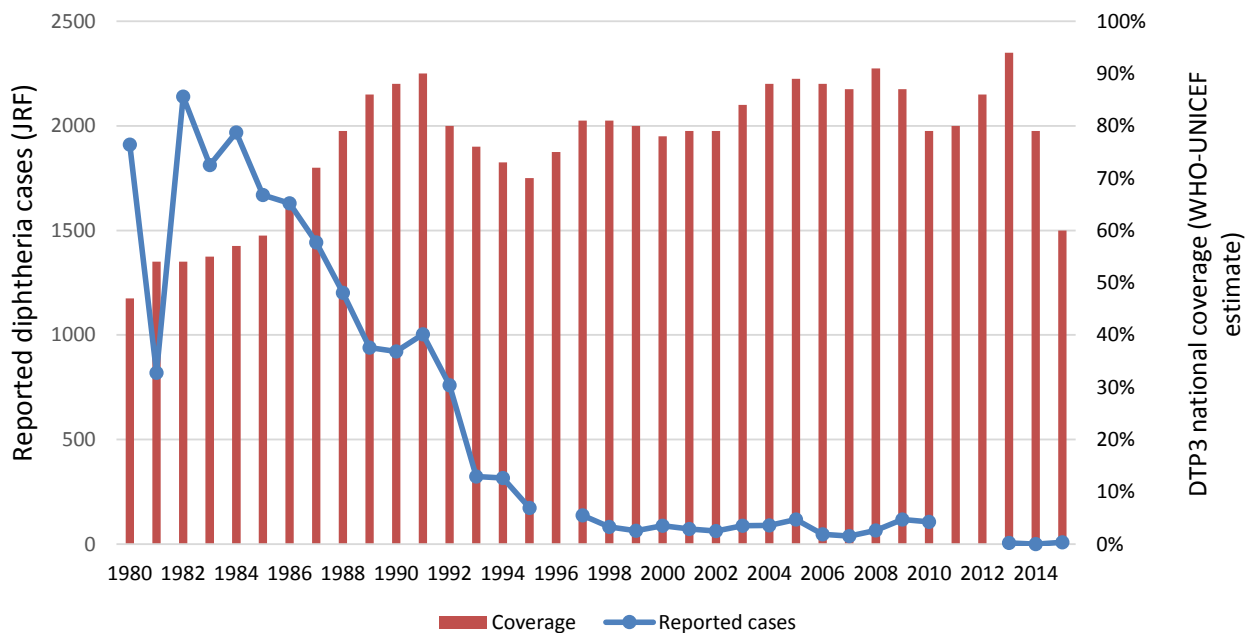
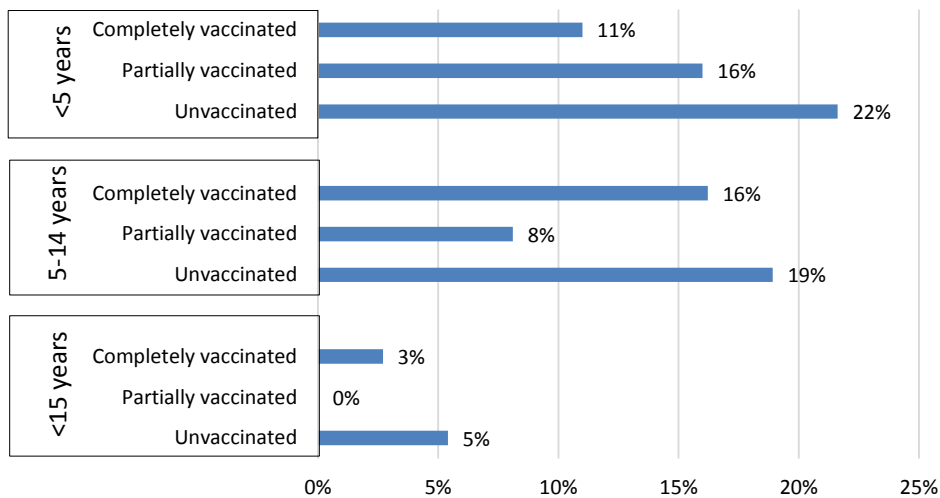


Figure 22: Diphtheria Incidence and DPT3 Coverage Trends - Philippines, 1980-2015

The 3 dose primary series is offered in the Philippines with no boosters, and DTP3 coverage has been over 80% since the late 1990s (Figure 21). National data reviewed spanned 2011-2016 (n=280 cases), and showed that 47% of cases were among completely vaccinated individuals. When linked age and vaccination data from 2016 were reviewed (n=37), 16% were among completely vaccinated individuals 5-14 years of age (Figure 22).



This shows the possibility of cases due to waning immunity; immunity is expected to wane during the school-age years if the last dose was given during the first year of life⁸. Only 3% of cases overall were among those aged 15 and over with a completed primary series. This could indicate past boosters from natural exposure, since incidence dropped sharply in the

Figure 21: Vaccination status and age of cases in the Philippines, 2016 (n=37)

Philippines in the early 1990s. However, these data are limited by a small sample size and must be interpreted with caution.

Main Findings:

1. Progress in decreasing diphtheria incidence worldwide has stalled over the past 10 years.
2. The South-East Asia Region, particularly India, is the major driver of global diphtheria incidence trends.
3. A wide variety of diphtheria vaccination schedules are used globally.
4. There are frequent discrepancies between diphtheria incidence reported to WHO compared to data published in the medical literature, making comparisons of published data with JRF data challenging.
5. Diphtheria incidence data are underreported by countries on the JRF, particularly in the African and Eastern Mediterranean regions.
6. Diphtheria data with information on age and/or vaccination status are incomplete and not equally representative across all regions.
7. Information on age and/or vaccination status of diphtheria cases is inconsistently reported and therefore difficult to aggregate and compare.
8. Most diphtheria cases occur in unvaccinated individuals, particularly in countries with higher case counts.
9. Age distributions of cases in countries with sporadic cases and countries with adult boosters reflect age shifts to the adolescent and adult populations. Countries with higher case counts or using different vaccination schedules have either not yet made this shift or may be in the process of doing so.
10. Countries with higher vaccination coverage had an increased percentage of cases over age 15 years compared to countries with lower vaccination coverage.

11. In countries in the dataset using the primary schedule only, the highest proportion of cases are in children 5-14 years of age among both unvaccinated and completely vaccinated individuals. This could be due to low vaccination rates and concentrated populations of children in a school setting, combined with potentially waning immunity after the primary series.
12. In analysis of vaccination status data across age groups, along with case studies of individual countries, there appears to be some evidence for cases in older vaccinated individuals due to waning immunity, especially in countries with higher current vaccination coverage.
13. Subnational coverage rates and age distributions, when available, can be important factors in explaining national incidence trends.

Disclaimers

The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

The views and opinions of the authors expressed herein do not necessarily state or reflect those of ECDC. The accuracy of the authors' statistical analysis and the findings they report are not the responsibility of ECDC. ECDC is not responsible for conclusions or opinions drawn from the data provided. ECDC is not responsible for the correctness of the data and for data management, data merging and data collation after provision of the data. ECDC shall not be held liable for improper or incorrect use of the data.

Acknowledgements

Dr. Colleen Scott, Dr. Nita Patel, and Dr. Tejpratap Tiwari reviewed abstracts and articles as part of the CDC Literature review workgroup; their contributions were critical to compiling the case data analyzed and interpreted in this report.

Dr. Eric Mast, Dr. Peter Bloland, Dr. Adam MacNeil, Dr. Stephen Hadler, Dr. Nita Patel, Dr. Colleen Scott, Dr. Tejpratap Tiwari, Dr. Kathleen Dooling, and Dr. Lina Nerlander of the US Centers for Disease Prevention and Control assisted by providing feedback and guidance on early drafts or sections of this report. Dr. Steve Cochi provided advice and guidance at the early stages of this analysis.

Dr. Thomas Cherian and Dr. Melanie Marti of WHO provided feedback and guidance on an early draft of this report.

Dr. Howard Gary provided statistical support and methodological guidance for the analysis.

The author would like to recognize international organizations and colleagues for sharing data from outbreak reports and surveillance systems for use in this analysis, particularly colleagues at the European CDC and Dr. Sudhir Joshi and Dr. Lucky Sangal of WHO-India.

References

1. Zakikhany K, Efstratiou A. Diphtheria in Europe: current problems and new challenges. *Future Microbiology* 2012; **7**(5): 595-607.
2. Diphtheria Reported Cases. In: Organization WH, (ed), 1980-2015.
3. Markina SS, Maksimova NM, Vitek CR, Bogatyreva EY, Monisov AA. Diphtheria in the Russian Federation in the 1990s. *Journal of Infectious Diseases* 2000; **181**(SUPPL. 1): S27-S34.
4. Galazka A. The Changing Epidemiology of Diphtheria in the Vaccine Era. *Journal of Infectious Diseases* 2000; **181**(Suppl 1): 52-59.
5. Galazka A. Implications of the diphtheria epidemic in the Former Soviet Union for immunization programs. *Journal of Infectious Diseases* 2000; **181** Suppl 1: S244-248.
6. Galazka A, Robertson SE. Immunization against diphtheria with special emphasis on immunization of adults. *Vaccine* 1996; **14**(9): 845-857.
7. Golaz A, Hardy IR, Strebel P, Bisgard KM, Vitek C, Popovic T *et al.* Epidemic diphtheria in the newly independent states of the former Soviet Union: Implications for diphtheria control in the United States. *Journal of Infectious Diseases* 2000; **181**(SUPPL. 1): S237-S243.
8. Tiwari T, Wharton M. Diphtheria Toxoid. In: Plotkin SA, Orenstein WA, Offit PA (eds). *Vaccines*, 6th edn. Elsevier Saunders: Edinburgh, 2013, pp 153-166.
9. Golaz A, Vitek C, Popovic T, Wharton M. Epidemiology of diphtheria in the 1990s. *Clinical Microbiology Newsletter* 2001; **23**(5): 33-37.
10. Scheifele DW, Ochnio JJ. *Diphtheria Update*. World Health Organization: Geneva, 2009.
11. Organization WH. WHO—recommended standards for surveillance of selected vaccine-preventable diseases. In. Geneva, 2014. pp 10-12.
12. Wagner KS, White JM, Lucenko I, Mercer D, Crowcroft NS, Neal S *et al.* Diphtheria in the postepidemic period, Europe, 2000-2009. *Emerging Infectious Diseases* 2012; **18**(2): 217-225.
13. Sutter RW, Stikas RA, Hadler SC, Fedson DS, Katz SL. Tetanus Immunization: Concerns about the Elderly and about Diphtheria Reemergence. *Journal of General Internal Medicine* 1994; **9**: 117-118.

14. Dravid MN, Joshi SA. Resurgence of diphtheria in Malegaon & Dhule regions of north Maharashtra. *Indian Journal of Medical Research* 2008; **127**(6): 616-617.
15. Sadoh AE, Oladokun RE. Re-emergence of diphtheria and pertussis: Implications for Nigeria. *Vaccine* 2012; **30**(50): 7221-7228. doi: <http://dx.doi.org/10.1016/j.vaccine.2012.10.014>
16. Mattos-Guaraldi AL, Moreira LO, Damasco PV, Hirata Junior R. Diphtheria remains a threat to health in the developing world--an overview. *Memorias do Instituto Oswaldo Cruz* 2003; **98**(8): 987-993.
17. Landazabal Garcia N, Burgos Rodriguez MM, Pastor D. Diphtheria outbreak in Cali, Colombia, August-October 2000. *Epidemiological bulletin* 2001; **22**(3): 13-15.
18. Quarterly communicable disease review January to March 2002. *Journal of Public Health Medicine* 2002; **24**(3): 232-238.
19. Disease watch. *Expert Review of Anti-Infective Therapy* 2003; **1**(3): 355.
20. Anima H, Malay M, Santanu H, Rajashree R, Sita C, Baran SA. A study on determinants of occurrence of complications and fatality among diphtheria cases admitted to ID & BG Hospital of Kolkata. *J Commun Dis* 2008; **40**(1): 53-58. e-pub ahead of print 2009/01/09;
21. Bonmarin I, Guiso N, Le Fleche-Mateos A, Patey O, Grimont Patrick AD, Levy-Bruhl D. Diphtheria: A zoonotic disease in France? *Vaccine* 2009; **27**(31): 4196-4200.
22. Nath B, Mahanta TG. Investigation of an outbreak of diphtheria in borborooah block of dibrugarh district, assam. *Indian Journal of Community Medicine* 2010; **35**(3): 436-438.
23. Perkins S, Cordery R, Nixon G, Abrahams A, Andrews J, White J *et al*. Investigations and control measures following a non-travel-associated case of toxigenic *Corynebacterium diphtheriae*, London, United Kingdom, December 2009-January 2010. *Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin* 2010; **15**(16): 22.
24. Saikia L, Nath R, Saikia NJ, Choudhury G, Sarkar M. A diphtheria outbreak in Assam, India. *The Southeast Asian journal of tropical medicine and public health* 2010; **41**(3): 647-652.
25. Chumachenko T, Podavalenko A, Glushkevich T. Spread of *Corynebacterium diphtheriae* in Ukraine during post-epidemic period. *Clinical Microbiology and Infection* 2011; **17**: S285.
26. Diphtheria Outbreak in an Urban City in Central Philippines, 2010. *EIS Conference International Night*; Atlanta, GA, 2011.

27. Niti T, Jignesh C, Himanshu N, Chintul S, Krupal M, Jaydeep D. Investigation of an outbreak of diphtheria in Dabela Village of Amirgagh Taluka and CHC, Banaskantha, Gujarat. *National Journal of Community Medicine* 2011; **2**(2): 196-200.
28. Rasmussen I, Wallace S, Mengshoel AT, Hoiby EA, Brandtzaeg P. Diphtheria outbreak in Norway: Lessons learned. *Scandinavian Journal of Infectious Diseases* 2011; **43**(11-12): 986-989.
29. Besa NC, Coldiron ME, Bakri A, Raji A, Nsuami MJ, Rousseau C *et al.* Diphtheria outbreak with high mortality in northeastern Nigeria. *Epidemiology and Infection* 2013; **142**(4): 797-802.
30. Phalkey RK, Bhosale RV, Joshi AP, Wakchoure SS, Tambe MP, Awate P *et al.* Preventing the preventable through effective surveillance: the case of diphtheria in a rural district of Maharashtra, India. *BMC public health* 2013; **13**: 317.
31. Wanlapakorn N, Yoocharoen P, Tharmaphornpilas P, Theamboonlers A, Poovorawan Y. Diphtheria outbreak in Thailand, 2012; seroprevalence of diphtheria antibodies among Thai adults and its implications for immunization programs. *The Southeast Asian journal of tropical medicine and public health* 2014; **45**(5): 1132-1141.
32. Rashid ZZ, Mohamed NA, Fong TS. A case of fatal diphtheria in a paediatric patient. *Internet Journal of Microbiology* 2015; **14**(1): 1-5.
33. Santos LS, Sant'Anna LO, Ramos JN, Ladeira EM, Stavracakis-Peixoto R, Borges LLG *et al.* Diphtheria outbreak in Maranhão, Brazil: Microbiological, clinical and epidemiological aspects. *Epidemiology and Infection* 2015; **143**(4): 791-798. doi: 10.1017/S0950268814001241
34. Doanh PV, Pham TD, Vu NL, Chu VT, Do THH, Nguyen TTH *et al.* An outbreak of diphtheria in K'Bang District, Gia Lai, Vietnam, October 2013 - July 2014. *International Journal of Infectious Diseases* 2016; **45**: 172.
35. Meera M, Rajarao M. Diphtheria in Andhra Pradesh-a clinical-epidemiological study. *International Journal of Infectious Diseases* 2014; **19**: 74-78.
36. Lumio J SP, Olander RM, Saxen H, Salo E. Fatal case of diphtheria in an unvaccinated infant in Finland. *Pediatric Infectious Disease Journal* 2003; **22**(9): 844-846.
37. Nandi RD, Mriganka; Browning, Simon; Purkayastha, Prabhati; Bhattacharjee, A K. Diphtheria: the patch remains. *The Journal of Laryngology and Otology* 2003; **117**(10): 807.

38. Krumina A, Logina I, Donaghy M, Rozentale B, Kravale I, Griskevica A *et al.* Diphtheria with polyneuropathy in a closed community despite receiving recent booster vaccination. *J Neurol Neurosurg Psychiatry* 2005; **76**(11): 1555-1557. doi: 10.1136/jnnp.2004.056523
39. Prasad KC KV, Shenoy S, Prasad SC. Upper Respiratory Tract and Cutaneous Diphtheria. *Indian Journal of Otolaryngology and Head and Neck Surgery* 2005; **57**(3): 250-252.
40. Sharma NCB, J N; Ranjan, Rajesh; Kumar, Rajnish. Bacteriological and epidemiological characteristics of diphtheria cases in and around Delhi- a retrospective study. *Indian Journal of Medical Research* 2007; **126**(6): 545.
41. Communicable disease and health protection quarterly review: July to September 2008. *J Public Health (Oxf)* 2008; **30**(4): 510-511. doi: 10.1093/pubmed/fdn090
42. Bitragunta S, Murhekar MV, Hutin YJ, Penumur PP, Gupte MD. Persistence of diphtheria, Hyderabad, India, 2003-2006. *Emerg Infect Dis* 2008; **14**(7): 1144-1146. doi: 10.3201/eid1407.071167
43. Fajolu IB TE, Egre-Okwaji MTC. Sporadic Emergence of Probable Cases of Diphtheria. *Nigerian Journal of Paediatrics* 2009; **36**: 87-90.
44. Fredlund H NT, Lepp T, Morfeldt E, Henriques Normark B. A case of diphtheria in Sweden, October 2011 *Eurosurveillance* 2011; **16**(50).
45. Mattos-Guaraldi AL, Damasco PV, Gomes DL, Melendez MG, Santos LS, Marinelli RS *et al.* Concurrent diphtheria and infectious mononucleosis: difficulties for management, investigation and control of diphtheria in developing countries. *J Med Microbiol* 2011; **60**(Pt 11): 1685-1688. doi: 10.1099/jmm.0.027870-0
46. Rousseau C BE, Broche B, Badell E, Guiso N, Laharie I, Patey O, Lévy-Bruhl D. Diphtheria in the south of France, March 2011. *Euro Surveill* 2011; **16**(19).
47. Lindhusen-Lindhé E DL, Berglund M. Imported laryngeal and cutaneous diphtheria in tourists returning from western Africa to Sweden, March 2012. *Euro Surveill* 2012; **17**(23).
48. Paul NI UR. Diphtheria in a 13 year old adolescent girl: Management challenges. *Nigerian Journal of Paediatrics* 2014; **41**(3): 247-250. doi: 10.4314/njp.v41i3,19
49. Garib Z, Danovaro-Holliday MC, Tavaréz Y, Leal I, Pedreira C. Diphtheria in the Dominican Republic: reduction of cases following a large outbreak. *Revista Panamericana de Salud Pública* 2015; **38**: 292-299.

50. Sane J ST, Widerström* M, Kauma H, Kaukoniemi U, Tarkka E, Puumalainen T, Kuusi M, Salminen M, Lyytikäinen O. Respiratory diphtheria in an asylum seeker from Afghanistan arriving to Finland via Sweden, December 2015. *Euro Surveill* 2016; **21**(2). doi: 10.2807/1560-7917
51. Sein C, Tiwari T, Macneil A, Wannemuehler K, Soulaphy C, Souliphone P *et al.* Diphtheria outbreak in Lao People's Democratic Republic, 2012-2013. *Vaccine* 2016; **34**(36): 4321-4326. doi: 10.1016/j.vaccine.2016.06.074
52. PAHO. Diphtheria Outbreak in Paraguay. *PAHO Immunization Newsletter* 2002; **24**(3): 6.
53. PAHO. Diphtheria Outbreak in Paraguay – An Update. *PAHO Immunization Newsletter* 2002; **24**(5): 7.
54. Lurie P SH, Tran P, Teacher C. Fatal Respiratory Diphtheria in a U.S. Traveler to Haiti. *MMWR* 2004; **52**(53): 1285.
55. PAHO. Diphtheria Outbreak in the Dominican Republic. *PAHO Immunization Newsletter* 2004; **26**(3): 1.
56. England PH. *Death in a child infected with toxigenic Corynebacterium diphtheriae in London*. Public Health England, 2008.
57. PAHO. Diphtheria Outbreak in Haiti, 2009. *PAHO Immunization Newsletter* 2009; **31**(6): 1.
58. Group NARW. Australia's notifiable disease status, 2011: Annual report of the National Notifiable Diseases Surveillance System. *Communicable diseases intelligence* 2013; **37**(4): E313-E393.
59. Control ECfDPa. *A case of diphtheria in Spain; Rapid Risk Assessment*. ECDC: Stockholm, 2015.
60. ECDC. A fatal case of diphtheria in Belgium. In: CDC E, (ed) *Rapid Risk Assessment*: ECDC, 2016. pp 1-10.
61. Flambées de diphtérie en Haiti-2004 et 2009. In: Haiti MSPP; PanAmerican Health Organization, 2010.
62. Tiwari T, Estivariz C, Lam E. Report on the Centers for Disease Control and Prevention mission to assist Indonesia's field epidemiology training program students to investigate and identify risk factors for the diphtheria outbreak in East Java during 2012. In, 2013.
63. Kaiser R. Diphtheria outbreak in KwaZulu-Natal, South Africa, March through June 2015. In: World Health Organization, 2015.
64. Informe de brote de Difteria en Venezuela. In: Panamerican Health Organization, 2016.

65. Report on Diphtheria Outbreak in Haiti. In: US Centers for Disease Control and Prevention, 2016.
66. Situation of Diphtheria in Punjab as on 12-11-2016. In: WHO Punjab, 2016.
67. Crucena JJD. Diphtheria in the Philippines. In: Republic of the Philippines, 2016.
68. Division EBotPHS. In: Republic of the Philippines, 2016.
69. Nguyen TD, Tran NVN, Vien QM, Do H, Nolen L. A diphtheria outbreak in a remote mountainous area of Quang Nam province, Viet Nam, 2015. In: World Health Organization, Vietnam; Pasteur Institute Nha Trong; US Centers for Disease Control and Prevention Vietnam, 2016.
70. Nihal A. Global and South-East Asia regional burden of diphtheria disease and strategies for control. In: WHO SEARO, 2016.
71. Sangal L, Joshi S. VPD Surveillance in India: A glance. In: WHO India, 2017.
72. The European Surveillance System (TESSy). In: Control ECfDPa, (ed), 2006-2016.
73. Organization WH. WHO-UNICEF estimates of DTP3 coverage In, 1980-2015.
74. Organization WH. Immunization schedule by disease In, 2016.
75. Control ECfDPa. Vaccine Schedule Search Tool. In. ECDC Network, 2016.
76. Vashishtha VM, Kumar P. 50 years of immunization in India: Progress and Future. *Indian Pediatrics* 2013; **50**: 111-118.
77. John TJ. Resurgence of diphtheria in India in the 21st century. *Indian Journal of Medical Research* 2008; **128**(5): 669-670.
78. Ramesh BM AF, Roy TK, Kanitkar T, Govindasamy P, Retherford RD. *National Family Health Survey (MCH and Family Planning), India 1992-1993*: Mumbai, 1995.
79. Roy TK AF, Kulkarni S, Kishor S, Gupta K, Mishra V, Nangia P, Retherford RD, Pandey A, Kumar S. *National Family Health Survey (NFHS-2), 1998-99: India*. Government of India: Mumbai, 2000.
80. *Multiple Indicator Survey 2000 India Summary Report*. Government of India: New Delhi, 2001.

81. Bhat PNM AF, Gupta K, Kishor S, Parasuraman S, Arokiasamy P, Singh SK, Lhungdim H. *National Family Health Survey (NFHS-3), 2005–06: India*. Government of India, 2007.
82. Health Information Management System. In: Government of India MoHaFW, (ed): Digital India, 2008-2016.
83. Bhavan N. *State Fact Sheet Bihar*. Government of India Ministry of Health and Family Welfare: Mumbai, 2015-16.
84. Bhavan N. *State Fact Sheet Kerala*. Government of India Ministry of Health and Family Welfare: Mumbai, 2015-2016.
85. Bhavan N. *State Fact Sheet Uttar Pradesh*. Government of India Ministry of Health and Family Welfare: Mumbai, 2015-2016.
86. Bhavan N. *State Fact Sheet Haryana*. Government of India Ministry of Health and Family Welfare: Mumbai, 20015-16.
87. Kantsone I, Lucenko I, Perevoscikovs J. More than 20 years after re-emerging in the 1990s, diphtheria remains a public health problem in Latvia. *Euro Surveill* 2016; **21**(48). doi: 10.2807/1560-7917.ES.2016.21.48.30414

Appendix A: Full search terms from literature review

Search Strategy (First search):

Database	Strategy	Run Date
Medline (OVID)	(Diphtheria/ AND Disease Outbreaks/) OR (diphtheria.ti AND (outbreak* OR cluster* OR epidemic*).ti,ab.) OR (diphtheria ADJ3 (outbreak* OR cluster* OR epidemic*)).ab.	11/4/2015
Embase (OVID)	(Diphtheria/ AND Disease Outbreaks/) OR (diphtheria.ti AND (outbreak* OR cluster* OR epidemic*).ti,ab.) OR (diphtheria ADJ3 (outbreak* OR cluster* OR epidemic*)).ab.	11/4/2015
Scopus	TITLE-ABS-KEY(diphtheria W/2 outbreak*)	11/4/2015

Search Strategy (Second search):

Database	Strategy	Run Date
Medline (OVID) 1946-	*diphtheria/ or diphtheria.ti,ab. AND Epidemics/ OR Disease Outbreaks/ OR (outbreak* OR cluster* OR epidemic*).ti,ab. AND Limit 2000-	06/20/2016
Embase (OVID) 1996-	*diphtheria/ or diphtheria.ti,ab. AND Epidemic/ OR (outbreak* OR cluster* OR epidemic*).ti,ab. AND Limit 2000-	06/20/2016
Global Health (OVID) 1973-	diphtheria/ OR diphtheria.ti,ab,sh. AND Epidemics/ OR (outbreak* OR cluster* OR epidemic*).ti,ab,sh. AND Limit 2000-	06/20/2016
CINAHL (Ebsco) 1982-	(MJ diphtheria) or (TI diphtheria) OR (AB diphtheria) AND (MH "Disease Outbreaks") OR (MH Epidemics) OR (TI (outbreak* OR cluster* OR epidemic*)) OR (AB (outbreak* OR cluster* OR epidemic*)) AND Limit 2000- ; Exclude Medline records	06/20/2016

Cochrane Library 1800-	[mh diphtheria] or diphtheria:ti,ab AND [mh "Disease Outbreaks"] OR [mh Epidemics] OR (outbreak* OR cluster* OR epidemic*):ti,ab AND Limit 2000-	06/20/2016
LILACS 1982-	Diphtheria AND (outbreak* OR cluster* OR epidemic*)	06/20/2016
Scopus 1960-	INDEXTERMS(Diphtheria) AND INDEXTERMS("disease outbreak*" OR epidemic*) AND (LIMIT-TO(PUBYEAR,2015) OR LIMIT-TO(PUBYEAR,2014) OR LIMIT-TO(PUBYEAR,2013) OR LIMIT-TO(PUBYEAR,2012) OR LIMIT-TO(PUBYEAR,2011) OR LIMIT-TO(PUBYEAR,2010) OR LIMIT-TO(PUBYEAR,2009) OR LIMIT-TO(PUBYEAR,2008) OR LIMIT-TO(PUBYEAR,2007) OR LIMIT-TO(PUBYEAR,2006) OR LIMIT-TO(PUBYEAR,2005) OR LIMIT-TO(PUBYEAR,2004) OR LIMIT-TO(PUBYEAR,2003) OR LIMIT-TO(PUBYEAR,2002) OR LIMIT-TO(PUBYEAR,2001) OR LIMIT-TO(PUBYEAR,2000)) AND (LIMIT-TO(DOCTYPE,"ar") OR LIMIT-TO(DOCTYPE,"re")) AND (LIMIT-TO(EXACTKEYWORD,"Diphtheria"))	06/20/2016

Appendix B: Definitions of variables and datasets in diphtheria epidemiology analysis	
Country type	
Higher case count	Countries reporting at least 10 diphtheria cases in at least 3 years of JRF incidence data between 2000 and 2015; Designation intended to be sensitive to include countries with possible endemic disease as well as those where imported cases lead to notable secondary transmission. (n= 225 cases; 19 countries in main review dataset)
Sporadic incidence	Countries who reported at least one diphtheria case between 2000 and 2015 but did not reach the threshold for higher case count countries; Designation intended to be specific for countries with occasional importations without wide secondary transmission and low likelihood of endemic disease. (n=10,694; 14 countries in main review dataset)
Vaccination schedule type	
Primary series only	3 doses of DTP or similar in infancy (“primary series”) are the only diphtheria-containing vaccines included in the national immunization schedule. (n= 1283 cases; 5 countries in main review dataset)
Last dose at <6y	In addition to the primary series, at least one booster dose of diphtheria-containing vaccine is on the national schedule. The last booster dose on the schedule is administered prior to 6 years of age. (n= 10,931; 5 countries in main review dataset)
Last dose at 6-17y	In addition to the primary series, at least one booster dose of diphtheria-containing vaccine is on the national schedule. The last booster dose on the schedule is administered between 6 and 17 years of age. (n= 872; 11 countries in main review dataset)
Adult boosters	In addition to the primary series and boosters, at least one dose of diphtheria-containing vaccine given at or after age 18 (n= 231; 12 countries in main review dataset)
Datasets	
Main review dataset	Main compilation of age and vaccination status of diphtheria cases worldwide constructed by principal investigator; all other datasets include a subset of these data. (n=10,919 cases)
5 Year dataset	Includes all cases with clear case age data around the 5 year cut-off (± 1 year). Excludes cases without age data. (n=10,385)
15 Year dataset	Includes all cases with clear case age data around the 15 year cut-off (± 1 year). Excludes cases without age data. (n=5,544)
Vaccine dataset	Includes all cases with clear data around vaccination status (cases clearly categorized as unvaccinated, partially vaccinated, completely vaccinated, or unknown vaccination status). Excludes cases without vaccination data. (n=1360)
Age and Vaccination status dataset	Includes data from sources that reported the vaccination status of cases within each age group. Includes data with age and vaccination status limitations. (n=3719)

Diphtheria vaccine

Review of evidence on vaccine effectiveness and immunogenicity to assess the duration of protection ≥ 10 years after the last booster dose.

April 2017

Background

Disease

Diphtheria is a disease caused by exotoxin-producing *Corynebacterium diphtheria* or –less frequently– *C. ulcerans*. There are 4 biotypes of *C. diphtheria* (*gravis*, *mitis*, *belfanti* and *intermedius*). The most common manifestation is respiratory diphtheria, which usually affects the pharynx and tonsils, though larynx or nasal tissues may be involved as well. In severe cases, obstructive pseudo-membranes in the upper respiratory tract (croup) can develop; other complications are myocarditis or polyneuritis. The overall case-fatality for diphtheria is 5–10%. Cutaneous manifestation of diphtheria can occur, resulting in indolent skin infection.

Passive and active immunization

Passive immunization via diphtheria antitoxin (DAT) of equine origin is highly efficacious in treating diphtheria though it is not a replacement for active immunization using diphtheria toxoid. Nevertheless, antitoxin is an important treatment of diphtheria and can reduce both morbidity and mortality. DAT should be administered as soon as possible after disease onset, once the toxin has entered the host cells it is unaffected by the antitoxin. The entire therapeutic dose should be administered at one time. The amount of antitoxin recommended varies between 20.000 and 120.000 units with larger amounts recommended for persons with extensive local lesions and with longer interval since onset. Global production and supply for equine antitoxin have been challenging as almost all traditional manufacturers have ceased their production. Novel approaches include the development of monoclonal antibodies to diphtheria toxin or development of recombinant modified diphtheria toxin receptor molecules to bind diphtheria toxin.¹ However, to date, no monoclonal antibody to diphtheria toxin is authorised for clinical use, therefore treatment still is dependent upon DAT.

Diphtheria toxoid is used for active immunization. Diphtheria vaccines are based on diphtheria toxoid, a modified bacterial toxin that induces protective antitoxin. Diphtheria toxoid is available in combination with tetanus toxoid (T) as DT (for use <7 years of age) or Td (for use ≥ 7 years of age), or with tetanus and pertussis vaccine (acellular=a, wholecell=w) as DT(a)(w)P or TdaP. Diphtheria toxoid may also be combined with additional vaccine antigens, such as polio (IPV), hepatitis B and *Haemophilus influenzae* type b.

In regard to the population level, it is believed that vaccine coverage of 80%–85% must be maintained in order to induce herd immunity/community immunity and reduce the threat of an outbreak.¹

Vaccine efficacy and effectiveness

No controlled clinical trial of the efficacy of the toxoid in preventing diphtheria has ever been conducted. There is, however, strong evidence from observational studies to support the effectiveness of vaccination, although effectiveness of diphtheria toxoid does not reach 100%:

- Halifax epidemic 1940-1941²: Among those immunized (most individuals had received 3 primary doses), the monthly incidence of diphtheria fell to 24.5 per 100,000 population, about one seventh of the rate in the unimmunized children during that same period (168.9 per 100,000).
- Britain 1943³: the rate of clinical diphtheria among the unimmunized was 3.5 times that among the immunized, and mortality was 25-fold greater.
- Eglin, Texas 1970⁴: In an outbreak only two of 205 fully immunized, exposed elementary schoolchildren acquired the disease.
- San Antonio, Texas 1970⁵: Vaccine efficacy was estimated at only 54%, though data were difficult to interpret.
- Yemen⁶: the protective efficacy of diphtheria toxoid was determined to be 87% among those who had received 3 or more doses by the case-control method.

The largest outbreak of the recent past was reported from the Russian Federation in the 1990. More than 115,000 cases and 3000 deaths were reported from 1990 to 1997.⁷ Most of the cases and deaths occurred among adults. Markina et al suggest that contributing factors included the accumulation of susceptible individuals among both adults and children, the probable introduction of a new biotype of *C. diphtheria* and social factors such as migrating populations. Vaccine quality, vaccine supply, or access to vaccine providers was assessed to not have significantly contributed to the epidemic.

- Ukraine 1992⁸: The effectiveness of three or more doses was 98.2% (95% confidence interval [CI], 90.3%-99.9%).
- Russia 1993⁹: The effectiveness of three or more doses was 96.9% (95% CI, 94.3%-98.4%), increasing to 99.0% for five or more doses (95% CI, 97.7%-99.6%).

Effect of vaccination on diphtheria carriage

Miller et al. 1970⁴ suggests that diphtheria vaccination prevents symptomatic infections, though it does not prevent carriage or spread of diphtheria. This hypothesis is based on throat swabs of 306 school children and staff during an outbreak investigation in Eglin Texas. *C. diphtheria* was isolated from 104 (34%) individuals of which 15 (14%) were cases and 89 (86%) were carriers. Of the 104 positive, 73 were fully, 28 inadequately and 3 not immunized. The presence of the phage (referring to the phage that induces toxin production in the bacterium) is thought to confer survival advantage to the bacterium by increasing the probability of transmission; transmission may be facilitated by local tissue damage resulting from the toxin.^{1,10,11} The United States Immunization Practices Advisory

Committee (ACIP) states, that immunization does not eliminate carriage of *C. diphtheriae* in the pharynx, nose or on the skin.¹²

WHO position paper on Diphtheria vaccine¹³ - Information on and recommended schedule

The current WHO recommendation which dates back from 2006 states that a primary series of DTwP- or DTaP-containing vaccines should be administered in 3 doses, starting as early as 6 weeks of age, and given with a minimum interval of 4 weeks. To compensate for the loss of natural boosting, industrialized countries should add childhood boosters of diphtheria toxoid to the primary immunization series of infancy. Booster doses should be given after the completion of the primary series. Boosting at the age of 12 months, at school entry and just before leaving school are all possible options, based on the local epidemiology. In addition to childhood (and adolescent) immunizations, WHO currently recommends that people living in low-endemic or non-endemic areas may require booster injections of diphtheria toxoid at about 10-year intervals to maintain life-long protection.

In light of WHO's Optimizing Immunization Schedules project, the comparative efficacy or effectiveness of different immunization schedules during the first 5 years of life against diphtheria were assessed.¹⁴ The review yielded, among other, the following results: For both diphtheria and tetanus, 2 primary doses resulted in substantially lower antitoxin mean titres than 3 primary doses. A birth dose prior to a 2,4,6-month primary schedule did not provide higher antitoxin geometrical mean concentrations (GMC) against diphtheria or tetanus between age 6 through 9 months or after a booster in the second year of life. The data suggest substantial increase in diphtheria and tetanus antibody due to booster vaccination at 18 months, following an initial 3,4,5-month primary schedule. The quality of the retrieved evidence varies.

The recently published WHO tetanus vaccine position paper¹⁵ recommends 6 doses (3 primary plus 3 booster doses prior to adolescence). As tetanus and diphtheria vaccines are frequently administered together, it would be programmatically advantageous to harmonize the schedules, granted that 6 doses of diphtheria vaccine prior to adolescence confer adequate levels of protection throughout adulthood.

Correlate of protection

On the basis of studies of diphtheria antitoxin levels early in the course of disease, persons with diphtheria antitoxin levels of less than 0.01 International Units (IU)/mL appear to be highly susceptible to disease, and higher levels are generally associated with progressively less severe symptoms.^{1,16,17,18,19}

Probably no level of circulating antitoxin confers absolute protection; Ipsen reported two cases of fatal diphtheria in patients with antitoxin levels above 30 IU/mL the day after onset of symptoms.¹⁶

Overall, the data allow some general conclusions regarding protective levels in most circumstances. An antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection, and 0.1 IU/mL is considered a protective level of circulating antitoxin. Levels of 1.0 IU/mL and greater are associated with long-term protection.²⁰

The WHO Immunological Basis Series for Diphtheria Immunization²¹ confirm that there is no sharply defined level of antitoxin that gives complete protection from diphtheria. A certain range of

variation must be accepted and the same concentration of antitoxin may give unequal protection in different persons. Other factors may influence vulnerability to diphtheria including the infecting dose and virulence of the diphtheria bacilli, and the general immune status of the person infected. Thus, an antibody concentration between 0.01 and 0.09 IU/mL may be regarded as giving basic immunity, whereas a higher titre may be needed for full protection.

The tissue culture neutralization assay is regarded as the most accurate *in vitro* procedure for measuring diphtheria antitoxin, whereas the ELISA and passive haemagglutination methods are known to be inaccurate in the low antitoxin range.²²

Duration of vaccine-induced protection

Both the diphtheria toxoid formulation and the schedule of administration affect the level of diphtheria antitoxin achieved and the duration of protection. After three doses of primary diphtheria toxoid immunization, most children achieve antitoxin titers greater than the minimally protective level.²³ However, in the absence of ongoing exposure, immunity wanes over time, requiring booster doses of diphtheria toxoid to maintain protective antitoxin levels. In the absence of a booster dose at 4 to 6 years, protection may not be maintained throughout the school-age years.

In countries with long-standing childhood immunization programs, adults who have neither been exposed to diphtheria nor received booster doses of diphtheria toxoid may become susceptible to diphtheria as a result of waning immunity.²³ During the outbreak in the former Soviet Union, waning of immunity was thought to contribute to the high incidence rate observed among adults. A large proportion of the population of adults, although seronegative, were previously primed by prior immunization or infection with toxigenic *C. diphtheriae*, as evidenced by development of protective titers after a single booster dose of toxoid.^{24,25,26,27}

Seroepidemiological data¹

The seroepidemiology of diphtheria in Czech Republic, Hungary, Ireland, Latvia, Luxembourg, Slovakia and Israel showed that increasing age is related to a gradual increase in seronegative subjects (< 0.01 IU/ml of diphtheria antitoxin antibodies). This may reflect waning immunity following childhood vaccination without repeated booster vaccinations in adults. Differences in seronegativity were also found according to gender. In subjects aged 1–19 years, geometric mean titres of antitoxin are clearly related to the different vaccination schedules used in the participating countries but most individuals between 1 and 19 years of age were seropositive (>0.01 IU/ml).²⁸

In Luxembourg, approximately 2.5% of individuals under the age of 20 were seronegative while 42% of individuals over the age of 40 years were seronegative. This finding supports the presumption that seronegativity tends to increase with age. A sex difference was found between males and females over the age of 50 years in Luxembourg but this difference was attributed to vaccinations given during military serviced which was made compulsory for males from 1944 to 1967.²⁹

¹ Presented here, a non-systematically retrieved, limited selection of seroepidemiological studies.

A study from Singapore³⁰ assessed that overall, 92.0% (95% CI: 91.1–92.9%) of 3293 adults aged 18–79 years had at least basic protection against diphtheria (antibody levels 0.01 IU/ml). Lowest seroprevalence was reported in those aged 50–59 (85.5%). Seroprevalence ranged from 87.7 to 92.7% among the elderly aged 60–79.

Age stratified data from China showed that the highest positivity rate of 97.63% was observed in children aged 1–4 years. The rates further decreased to 83.80% at 10–14 years and 73.64% at 15–19 years of age, despite a diphtheria booster dose at 15 years. The positivity rates were around 52% in those aged 25–29 years. The lowest level of 34.11% was observed in subjects older than 40 years.³¹

Objective

In view of the recent diphtheria outbreaks in South-East Asia such as in Lao People's Democratic Republic from 2012–2013³², in India³³ 2015 and 2016, Myanmar 2016, Philippines 2016 and Malaysia 2016 as well as a recent shortages of diphtheria antitoxin and cases³⁴ reported from the WHO European Region, the Strategic Advisory Group of Experts (SAGE) on Immunisation requested to review the available data and assess the need to revisit the current recommendation.

Objective of this literature review was to assess long-term diphtheria vaccine effectiveness (VE) or level of immunogenicity conveyed by doses beyond the three-dose primary immunization and a 3 dose childhood/adolescent booster dose schedule in order to inform on the afforded duration of vaccine-induced protection and to allow for the assessment of the need for diphtheria (decennial) booster doses. This review will inform the deliberations of SAGE at the April 2017 meeting and facilitate the formulation of related recommendations on the use of the vaccine. These recommendations will be reflected in an update of the current 2006 diphtheria vaccine WHO position paper.¹³ Based on the results, it is aimed to harmonize recommendations on the vaccination schedule across the WHO diphtheria vaccine, pertussis vaccine and tetanus vaccine position paper.

Methods

To identify relevant literature, the following search strategy to answer the specific Population (P), Intervention (I), Comparison (C), Outcome (O)- question guided the review.

- **Population:** Immunocompetent children and adults.
- **Intervention:** Vaccination with diphtheria toxoid (-containing) vaccination
- **Comparison:** No vaccination
- **Outcomes:** Cases of respiratory diphtheria

PICO Question: What is the duration of continued protection (effectiveness) of diphtheria vaccination beyond the primary immunization schedule (≥ 3 doses) against cases of respiratory diphtheria conveyed by a specific schedule of diphtheria toxoid (-containing) vaccination and 3 booster doses until adulthood.

A systematic search was conducted using the National Library of Medicine's online search utility PubMed. The search terms can be found in Annex 1. No restrictions were made to range of years, thus the start date was from the beginning of the candidate database to January 2017. No language restrictions were made. In addition, references of eligible reviews were screened to identify further

publications. The literature review considered published, peer-reviewed literature as the primary source of data. All study designs that allowed the assessment of vaccine effectiveness were included (RCTs, case control studies, cohort studies, case-cohort studies). Studies were included when they reported VE by time (or time-interval) since vaccination being 10 years or more among individuals who received at least the primary series (i.e. 3 vaccine doses) plus 3 booster doses during childhood and/or adolescence.

Due to insufficient data being retrieved from the initial search focusing on diphtheria-related clinical endpoints to guide SAGE's decision-making process, the search was expanded to include serological endpoints. Studies were included if they provided any estimate of vaccine-induced serum antibodies levels provided by primary immunization (i.e. 3 vaccine doses) plus 3 booster doses during childhood and/or adolescence and the interval to the receipt of at least primary immunization of diphtheria containing vaccine was ≥ 10 years. The search terms can be found in Annex 1.

- **Population:** Immunocompetent children and adults.
- **Intervention:** Vaccination with diphtheria toxoid (-containing) vaccination
- **Comparison:** No vaccination, or different duration between vaccination and serological testing
- **Outcomes:** Diphtheria serum antibody levels/ seroprevalence

PICO Question: What is the duration of continued seroprotection of diphtheria vaccination (≥ 10 years) conveyed by a specific schedule of diphtheria toxoid (-containing) vaccination which is comprised of at least 3 vaccine doses (primary series) and 3 booster doses until adulthood.

For both searches, article titles and abstracts were manually examined by two reviewers (OW and MM) and appropriate articles were selected for further review.

Extracted variables included: place, year, number of subjects included in study, any available measure of age, number of diphtheria vaccine doses and time since immunization in the affected individuals, vaccine used and calculated VE (See Annex 2). For the review on seroprotection information on the diagnostic test, the cut-off level as well as antibody levels or proportion of study population being seroprotected were abstracted. The results of this review are provided to SAGE ahead of the April 2017 meeting.

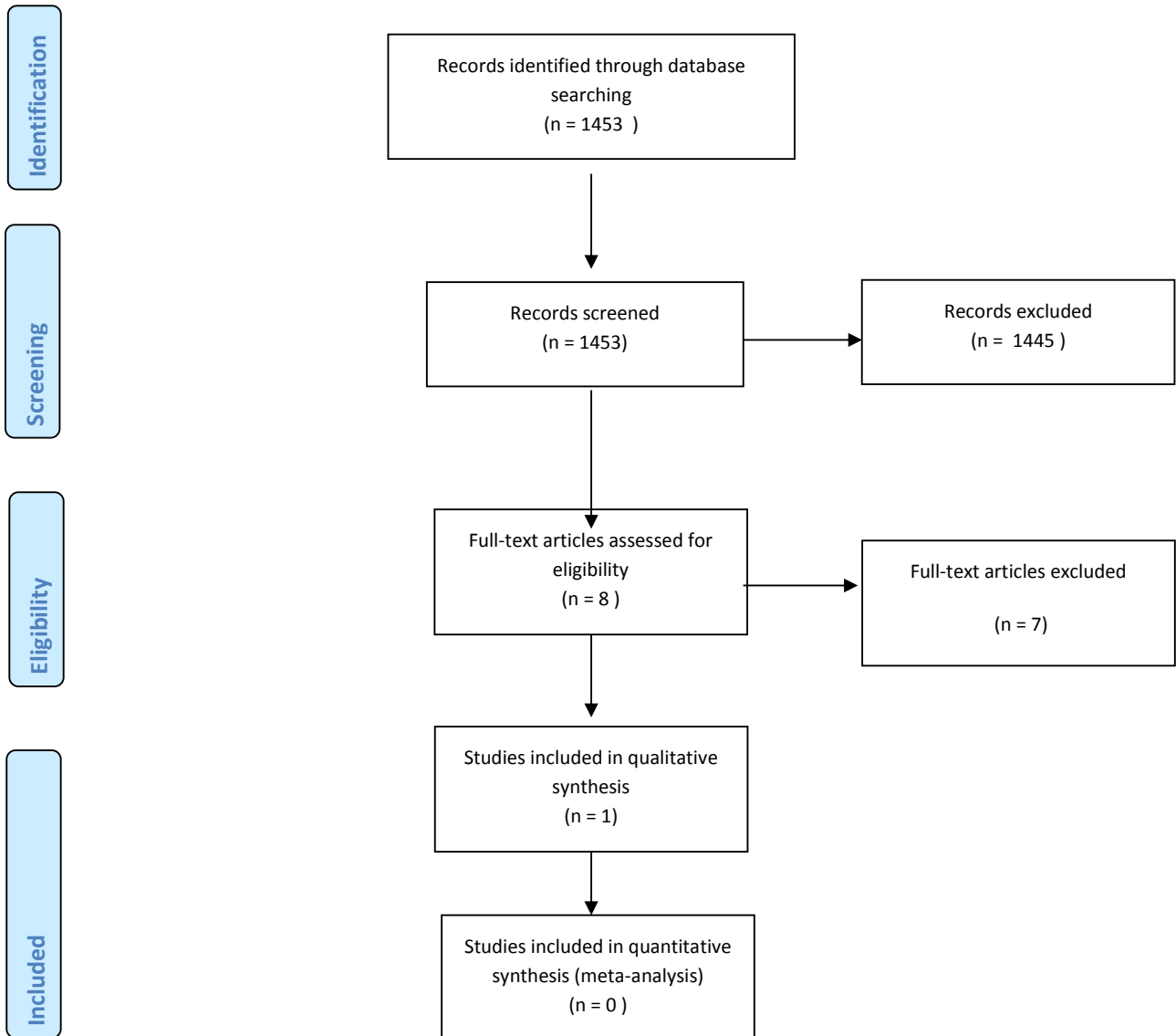
Results

Effectiveness data

The search on the effectiveness and duration of protection yielded a total of 1453 reviews. After screening of titles and abstracts, 8 full-text articles^{35,36,37,38,39,40,41,42} were assessed for eligibility of which 1³⁶ was included in the qualitative synthesis. None of the studies fulfilled the inclusion criteria and provided an effect estimate on the outcome of continued (>10 years) duration of protection conveyed by a specific schedule of diphtheria-containing vaccines, though the results of 1 study was included for descriptive analysis (see Figure 1).

Brennan et al. 2000³⁶ calculated the matched odds ratio (OR) for time since last dose being 0-4 years (reference) or ≥ 5 years in adults 40–49 years of age during the Russian diphtheria epidemic of the 1990s. This age-group in 1995 were born during 1946–1955 and grew up during a period in the Russian Federation when routine childhood immunization had begun but coverage was not complete and circulation of *C. diphtheria* was diminishing, hence were the least likely of any age group to be immunologically protected by either natural infection or vaccination. Cases who had not received any dose in the previous 10 years were excluded. The OR for cases having received the last dose of vaccine ≥ 5 years in the past was 12.7 (95%CI: 1.5–106.6) when comparing to cases who received their last dose 0-4 years ago. However, it was unknown if the cases had received during their childhood a complete primary series of three vaccine doses and potentially also booster doses, or if they were completely naïve. Therefore, this study does not provide any evidence in respect to the duration of protection following 6 doses of diphtheria toxoid (-containing) vaccines.

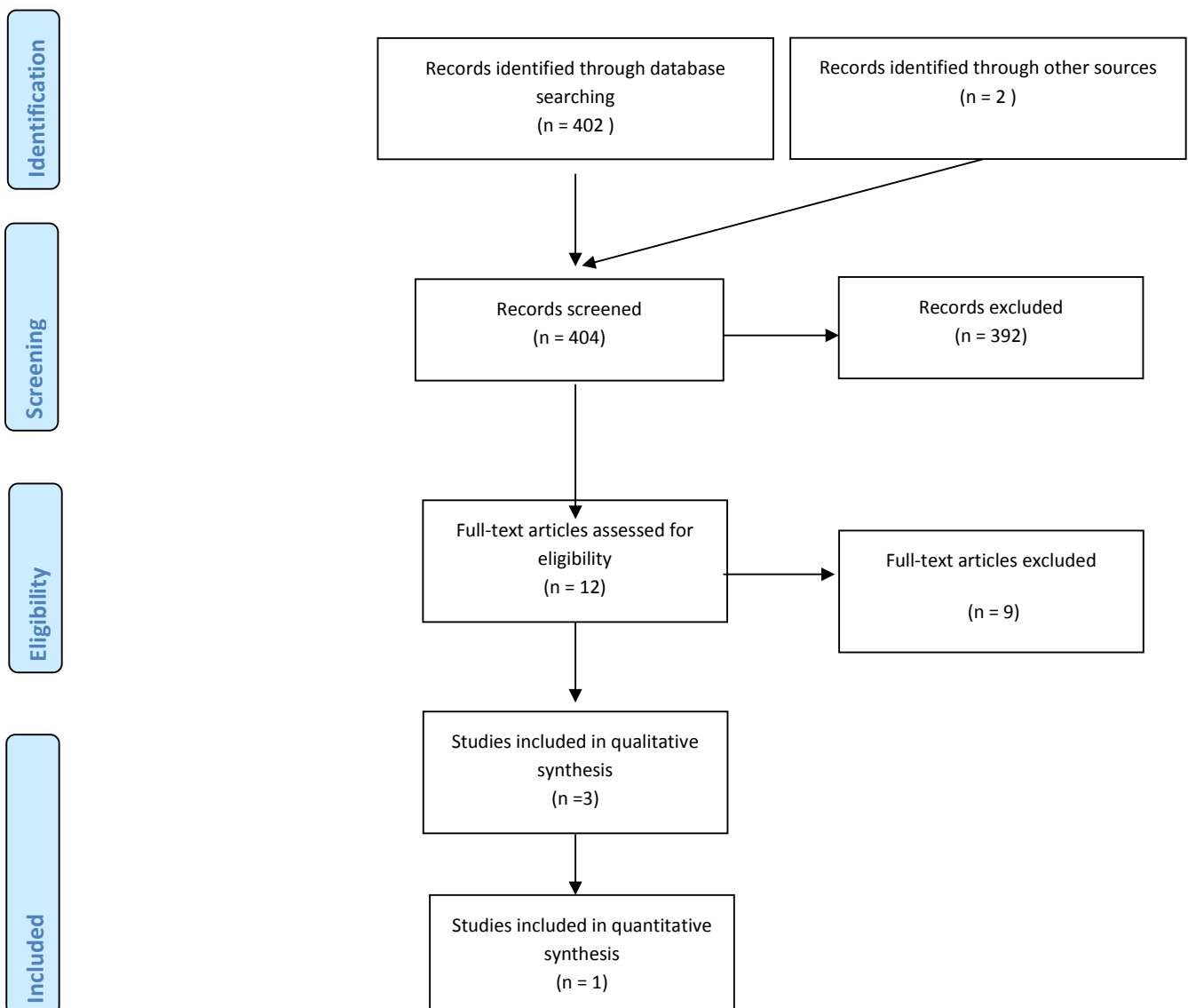
Figure 1: PRISMA Flow Diagram



Immunogenicity data

The systematic review of literature on the immunogenicity conferred by diphtheria-containing vaccine yielded a total of 402 publications of which 10 were included for full text review^{43,44,45,46,22,47,48,49,50,51}. The search was complemented by screening of references as well as a systematic review of literature conducted by the United States Center for Disease Control and Prevention (US CDC), identifying diphtheria serosurvey studies which yielded two additional studies^{52,53} for full text consideration. Of these 12 publications, only one publication⁴⁸ was considered to meet the inclusion criteria, by providing information on immunogenicity levels in relation to time since the receipt of a 3 primary and 3 booster schedule until adolescence (see Figure 2). Two additional studies^{22,44} provided some information on level of protection, though no direct evidence on the number of vaccine doses in relation to the time since last vaccination was provided. One study⁵² was identified as supportive evidence and is described below.

Figure 2: PRISMA Flow Diagram



Swart et al 2016⁴⁸ present the results of two population-based cross-sectional representative seroepidemiological studies performed in the Netherlands in 1995/1996 and in 2006/2007. Antibody levels below 0.01 international units per ml (IU/ml) were considered as non-protective, levels of 0.01 IU/ml–0.1 IU/ml were considered to provide basic protection and levels above 0.1 IU/ml were considered to provide full protection against diphtheria. Data were provided on the persistence of diphtheria IgG antibody in 10 to 34 and 10 to 39 year old individuals, in the national sample of the 1995/1996 serosurvey (n = 961) and 2006/2007 serosurvey (n = 971), who were completely immunized against diphtheria according to the national immunization programme (NIP) (3 infant doses followed by booster doses at 11 months, 4 years and 9 years of age), without evidence of re-vaccination. Overall, 0.8% (95%CI: 0.3-1.4) within the 1995/1996 serosurvey and 3.5% (95%CI: 2.3–4.7) within the 2006/2007 serosurvey were not protected (seroprevalence <0.01 IU/ml). The highest percentages, 5.8% (95%CI: 0.0–12.1) and 8.3% (95%CI: 1.9–14.7), of individuals below the protective threshold (<0.01 IU/ml) were seen in the age group from 30-34 years within the 1995/1996 serosurvey and 2006/2007 serosurvey, respectively.

When combining the data from both serosurveys, within the age group of 30-34 years of age, 7.3% (95%CI: 0.0-13.7) remain below the protective threshold (Table 1).

Table 1: Age seroprevalences (%) of diphtheria antibody in 10 to 39 year old individuals, combining the national samples of the 1995/1996 serosurvey (n = 961) and 2006/2007 serosurvey (n = 971), who were completely immunized against diphtheria according to the NIP, without evidence of revaccination.

Age (years)	N	<0.01 IU/ml (%)	(95% CI)	≥0.01 IU/ml (%)	(95% CI)
<u>1995/1996 and 2006/2007 serosurvey</u>					
Overall	1932	2.2	(1.5-2.5)	97.8	(97.5-98.5)
10–14	738	0.5	(0.0-1.0)	99.5	(98.9-100)
15–19	499	1.2	(0.3-2.2)	98.8	(97.8-99.8)
20–24	335	3.9	(1.8-6.0)	96.1	(94.1-98.2)
25–29	199	4.0	(1.3-6.8)	96.0	(93.3-98.7)
30–34	124	7.3	(2.7-11.8)	92.7	(88.2-97.3)
35–39*	37	5.4	(0.0-13.7)	94.6	(87.3-100)

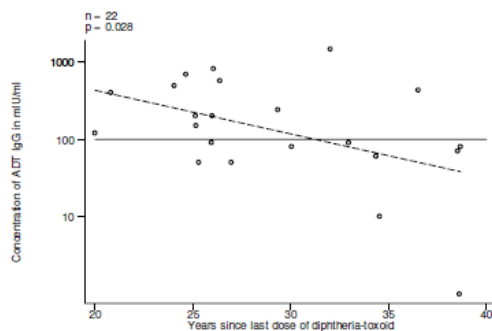
*Data from 2006/2007 serosurvey only.

The quality of the retrieved evidence was assessed using the GRADE approach (see Annex 2).

Goncalves et al 2007⁴⁴ assessed the levels of diphtheria and tetanus specific IgG of Portuguese adult women, before and after vaccination with adult type Td and the duration of immunity following vaccination. Twenty-two women had begun their vaccination in childhood with DTP before the age of 7 (n=20) or with DT between 7-9 years (n=2). These women were born between 1956 and 1973 and - at time of study recruitment- less than 50 years of age. All women had completed their primary immunization (National schedule in Portugal since 1966: 3 primary doses, and booster doses at 18-24 months and 5-6 years. Since 2001: Td is recommended for decennial booster doses). In these 22 women, the last dose of diphtheria toxoid was received 20-39 years ago. On univariate analysis, anti-diphtheria toxin (ADT) IgG levels increased with the number of doses of diphtheria toxoid received (p = 0.013). The laboratory analysis were performed using a commercial enzyme immunoassay. ADT IgG levels ≥100 mIU/ml were considered protective, as recommended in the WHO Immunological

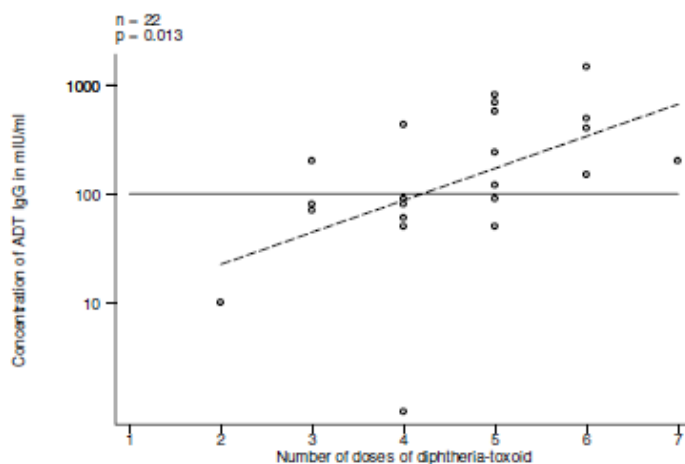
Basis Series for Diphtheria Immunization²¹ when EIA technique is performed; according to that threshold, women were classified as "immune" or "susceptible" to diphtheria. Additionally, we considered those with levels ≥ 1000 mIU/ml as having "long-term protection". All women who had received 6+ were immune (threshold level of 100 mIU/ml). On univariate analysis ADT IgG levels were also associated with time since last dose ($p = 0.028$), all susceptible women had received diphtheria toxoid more than 25 years before. For those who began vaccination in childhood with DPT/DT, the total number of doses and time since last vaccination were determinant factors; in the 20 women who had received a complete DTP primary series (3 doses) during childhood and at least one booster, no susceptibles were observed before 20 years had elapsed from the last dose. (Figure 3)

Figure 3: ADT IgG levels, by time since last dose of diphtheria-toxoid, in pre-vaccination sera of women who had been vaccinated with diphtheria-toxoid. Regression line (stippled) and threshold level of 100 mIU/ml (from Goncalves 2007 et al).



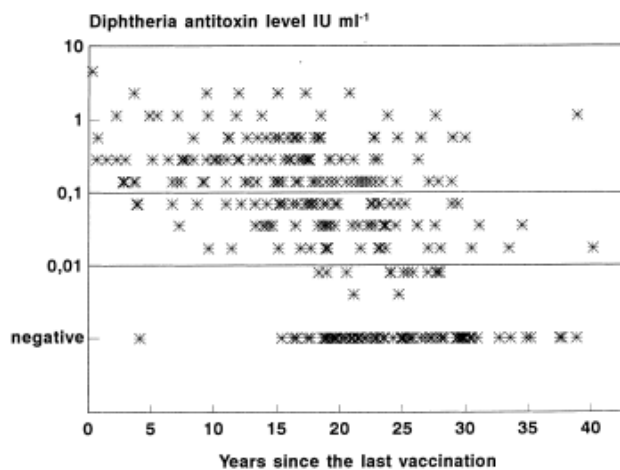
Of those women, having received 6 or more doses, all had ADT IgG levels above the protective threshold. (Figure 4)

Figure 4: ADT IgG levels, by number of doses of diphtheria-toxoid administered, in pre-vaccination sera of women who had been vaccinated with diphtheria toxoid. Regression line (stippled) and threshold level of 100 mIU/ml (from Goncalves 2007 et al).



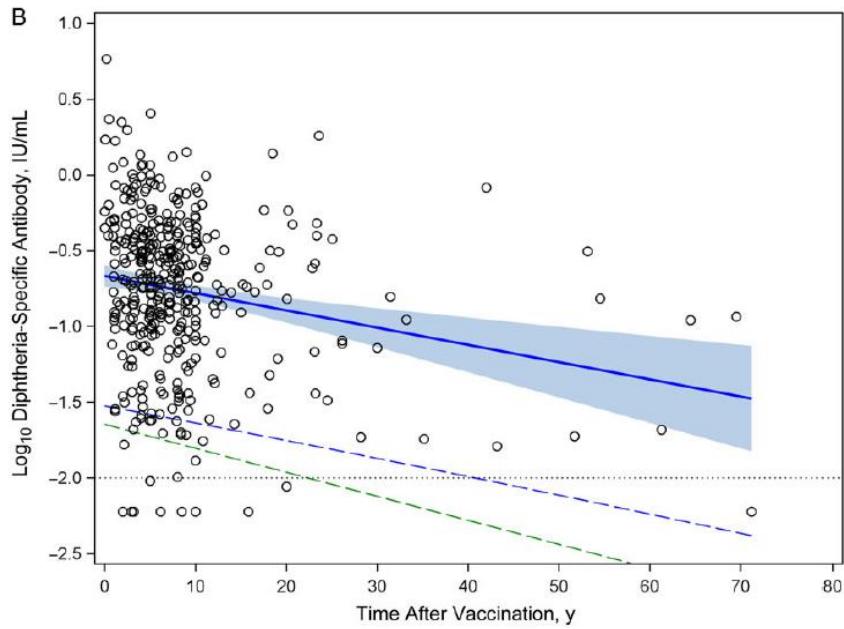
Hasselhorn et al 1998²² recruited a total of 287 healthy adults (154 women and 133 men: mean age 26.4 years; range 17–54, ± 6.1) in Germany. Participation was limited to those for whom a complete record of diphtheria vaccination was available and who had received basic immunization. The participants had received a mean of 4.4 diphtheria vaccinations (range: 3–8, ± 1.1). The last vaccination being 19.2 years (mean) before (range: 3 months–43.0 years, ± 7.8 years). Ninety (31.4%) out of the 287 participants were ‘probably susceptible’ to diphtheria, 76 (26.5%) had ‘basic protection’ and 121 (42.2%) had ‘fully protective’ antitoxin levels. The results suggest that diphtheria antitoxin levels wane with the time elapsed since the last vaccination, but that –with only one exception- all individuals had protective antibody levels in the 15 years after the last vaccine dose (See Figure 5). However, the paper does not provide any information on the total number of vaccine doses among individuals who had no or non-protective antibodies levels >15 years after the doses.

Figure 5: Diphtheria antitoxin levels by time interval since last vaccination. Stages: $<0.01 \text{ IU ml}^{-1}$ =probably susceptible; $0.01\text{--}0.1 \text{ IU ml}^{-1}$ =basic protection; $\geq 0.1 \text{ IU ml}^{-1}$ =full protection. GMT= 0.04 IU ml^{-1} ; negative values treated as 0.001. $n_{\text{total}}=287$ (from Hasselhorn 1998 et al.).



One study was identified as supportive evidence in regard to the research question. Hammarlund et al 2016⁵² performed a cross-sectional analysis of serum antibody titers in 546 adult subjects living in the United States. Approximately 99% of subjects <60 years of age (and 97% of the overall population) showed diphtheria-specific antibody responses that were above the protective level of 0.01 IU/mL. Based on analysis of antibody levels as a function of time after vaccination, diphtheria-specific immunity declined in the model with a 27-year half-life (95% CI: 18–51 years) (see Figure 6). Also in this study the exact number of previous vaccine doses is unknown.

Figure 6: Humoral immunity to diphtheria as a function of age and time after vaccination. Diphtheria-specific serum antibody responses were measured in adult subjects and plotted versus age (A) or time after vaccination (B). Dotted line in each panel represents level of antibody required for protection, equivalent to 0.01 IU/mL. B, Solid blue line is the fitted regression line representing the antibody half-life decay rate, and the shaded blue region represents the upper and lower bound of 95% confidence interval (CI) for the antibody half-life estimation. Dashed blue line represents a 1-sided lower bound 95% CI based on a 27-year half-life and indicates when diphtheria-specific antibody titers would decline to 95% seroprotection by crossing the protective threshold of 0.01 IU/mL (ie, $-2 \log_{10}$ IU/mL) at 42 years after vaccination. Dashed green line is based on an estimated 19-year half-life⁵⁴ and indicates that 95% of the population will remain protected against diphtheria for 30 years after vaccination (from Hammarlund et al 2016).



Conclusions

No data in observational studies on long-term clinical effectiveness of diphtheria-containing vaccine could be retrieved, though limited evidence suggests that the risk of disease increased with time since last vaccination but clearly also depends on the total number of received vaccine doses.³⁶

Only one study retrieved assessed the duration of protection from diphtheria vaccination within the outbreak setting of the Russian Federation diphtheria epidemic of the 1990s.³⁶ Adults having received the last dose ≥ 5 years in the past was associated with a higher OR for being a case (12.7 (95%CI: 1.5–106.6)). Certain limitations apply, that the duration of protection was assessed for having received the last dose of diphtheria vaccine only ≥ 5 years vs ≥ 10 years in the past and no information was provided on the total number of doses received as outlined in the inclusion criteria. Further, the small sample size did not allow distinguishing between time since last dose and number of doses because both variables were highly correlated.

Given the limited evidence in respect to the effectiveness of the vaccine in conferring long-term protection, the systematic review assessed the levels of protective immunogenicity conferred by diphtheria vaccination.

Data on the duration of seroprotection from a large representative population study from the Netherlands, using a complete 3-dose primary series plus 3-dose booster series prior to adolescence⁴⁸ indicate that this schedule confers a very high seroprevalence above the protective threshold (≥ 0.01 IU/ml) up to 39 years of age and potentially longer. A seroprevalence of 94.6% (95%CI: 87.3–100) was observed even in this oldest age group (up to age 39). When combining the two serosurvey studies from 1995/1996 and 2006/2007, a high level of protection with narrow confidence intervals could be observed. Nevertheless, certain caveats remain in regard to combining both two cohorts. The schedule with six diphtheria vaccinations has been in use for both cohorts, however, the combination vaccines used in the NIP in the Netherlands have changed several times in composition and of manufacturer.⁵⁵ In 2003 Haemophilus influenza (Hib) vaccine was added to the DTwP-IPV vaccine for infants (DTwP-IPV/Hib) and in 2005 the infant whole-cell pertussis vaccine was replaced by an acellular pertussis vaccine (DTaP-IPV/Hib).⁵⁶ In 2006 a seven-valent pneumococcal vaccine conjugated to a non-toxic, fully immunogenic mutant of diphtheria toxin (CRM197) was added to the NIP at two, three, four, and 11 months of age for all children born in or after April 2006. In addition, in July/August 2006, acellular pertussis vaccine was added to the booster combination vaccine for 4-year-olds (DTaP-IPV).

Given the likely low number of reported cases of diphtheria in the Netherlands in the past years,³⁴ one can assume limited circulation of the disease and hence the limited chance of exposure conveying natural boosting. Therefore, the observed high levels of protective immunity are most likely to be attributable to the 6 dose immunization schedule used in the country.

These data suggest, that the immediate administration of decennial booster doses following a 3 dose primary and 3 dose booster schedule may not be needed however this needs to be monitored long-term with increasing life expectancy in large parts of the world. No data could be retrieved on the duration of protection conferred by this schedule beyond 39 years of age. This evidence is supported by a seroprevalence study from the United States, which modelled a half-life for diphtheria-specific immunity of 27-year (95% CI: 18–51 years); however in this study it cannot be

excluded that some individuals had received some or all decennial booster doses according to the United States recommendations.

Based on supportive evidence⁵² and on selected seroepidemiological studies^{28,29,30,31}, in some settings, immunity gaps may exist in older age groups, either due to waning immunity or due to no or incomplete vaccination. It remains to be demonstrated whether the 6-dose schedule provides live-long protection to the vast majority of vaccinated individuals or if revaccination of older age groups may be needed.

Recommendations

To harmonize the vaccination schedules across the diphtheria, tetanus and pertussis vaccine position papers, SAGE should consider the following draft recommendations:

1. A primary series of 3 doses of diphtheria-containing vaccine (completed by 6 months of age if possible) should be administered;
2. Three booster doses of diphtheria-containing vaccine should be administered in childhood and completed by adolescence.
3. The booster doses of diphtheria-containing vaccine should be given at: 12–23 months of age; 4–7 years of age; and 9–15 years of age.
4. Immunity gaps may exist in the older populations due to waning immunity or non-vaccination. Further research is required to fully assess the duration of protection against diphtheria in the older populations.

Annex 1

Search Strategy 1:

(Vaccin* OR immunisation OR immunization)

AND (Diphtheria)

AND (efficacy) OR (effectiv*)

Search Strategy 2:

((Vaccin* OR immunisation OR immunization)

AND (Diphtheria))

AND ((antibod*) OR (seroprotecti*) OR (serology) OR (immunogenicity) OR (immunity)

AND (waning OR duration of protection OR durability OR decay OR long-term OR continued OR lasting OR decline))

Annex 2

GRADE Table : Duration of continued seroprotection

Population: Immunocompetent children and adults.

Intervention: Vaccination with diphtheria toxoid (-containing) vaccination

Comparison: No vaccination, or different duration between vaccination and serological testing

Outcomes: Serum antibody levels/ seroprevalence

PICO Question: What is the duration of continued seroprotection of diphtheria vaccination (≥ 10 years) conveyed by a specific schedule of diphtheria toxoid (-containing) vaccination which is comprised of at least 3 vaccine doses (primary series) and 3 booster doses until adulthood.				
		Rating	Adjustment to rating	
Quality Assessment	No of studies/starting rating		1 observational ²	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			2
Summary of Findings	Statement on quality of evidence		Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.	
	Conclusion		6 doses of diphtheria-containing vaccine in childhood and adolescence, without administration of booster doses confer high levels of seroprotection up until 39 years of age and potentially longer.	

Reference

Swart et al. Long-Term Protection against Diphtheria in the Netherlands after 50 Years of Vaccination: Results from a Seroepidemiological Study. PLoS ONE 11(2): e0148605

² Swart et al. suggests that 6 doses of diphtheria-containing vaccine, administered in infancy and childhood, induce seroprevalence levels above the protective threshold (≥ 0.01 IU/ml) in 92.7% (95%CI: 88.2%-97.3%) for both national serosurveys combined (1995/1996 and 2006/2007) in persons aged 30-34 years and 94.6% (95%CI: 87.3%-100%) for persons aged 35-39 years (2006/2007 serosurvey only).

Reference list

- ¹ Plotkin et al. *Vaccine*. 6th Edition. Elsevier.
- ² Wheeler S.M., Morton A.R.: Epidemiological observations in the Halifax epidemic. *Am J Public Health*. 32:947-956 1942
- ³ Stuart G.: A note on diphtheria incidence in certain countries. *Br Med J*. 2:613-615 1945
- ⁴ Miller L.W., Older J.J., Drake J., et al.: Diphtheria immunization: effect on carriers and the control of outbreaks. *Am J Dis Child*. 123:197-199 1972
- ⁵ Marcuse E.K., Grand M.G.: Epidemiology of diphtheria in San Antonio, Texas, 1970. *JAMA*. 224:305-310 1973
- ⁶ Jones E.E., Kim-Farley R.J., Algunaid M., et al.: Diphtheria: a possible foodborne outbreak in Hodeida, Yemen Arab Republic. *Bull World Health Organ*. 63:287-293 1985
- ⁷ Svetlana S. Markina, Nina M. Maksimova, Charles R. Vitek, Erika Y. Bogatyreva, and Anatoly A. Monisov. Diphtheria in the Russian Federation in the 1990s. *J Infect Dis*. (2000) 181 (Supplement 1): S27-S34.
- ⁸ Chen R.T., Hardy I.R.B., Rhodes P.H., et al.: Ukraine, 1992: first assessment of diphtheria vaccine effectiveness during the recent resurgence of diphtheria in the former Soviet Union. *J Infect Dis*. 181 (Suppl. 1):S178-S183 2000
- ⁹ Bisgard K.M., Rhodes P., Hardy I.R.B., et al.: Diphtheria toxoid vaccine effectiveness: a case-control study in Russia. *J Infect Dis*. 181 (Suppl. 1):S184-S187 2000
- ¹⁰ Pappenheimer AM, Gill DM. Diphtheria. *Science* 1973; 182: 353–8.
- ¹¹ Collier RJ. Diphtheria toxin: mode of action and structure. *Bacteriol Rev* 1975; 39: 54–85.
- ¹² Recommendations of the Advisory Committee on Immunization Practices (ACIP). Diphtheria, Tetanus, and Pertussis: Recommendations for vaccine use and other preventive measures. *MMWR* 1991;40(RR-10):1-28.
- ¹³ Diphtheria vaccine WHO position paper. *WER*. No. 3, 2006, 81, 21–32.
<http://www.who.int/wer/2006/wer8103.pdf?ua=1>, accessed March 2017
- ¹⁴ Comparative efficacy/effectiveness of schedules in infant immunisation against pertussis, diphtheria and tetanus: Systematic review and meta-analysis. Part 1: Diphtheria and tetanus vaccines. http://www.who.int/immunization/sage/meetings/2015/april/5_Report_D_T_140812.pdf?ua=1, accessed Feb 2017
- ¹⁵ Tetanus vaccines: WHO position paper – February 2017. *WER*. No 6, 2017, 92, 53–76.
<http://apps.who.int/iris/bitstream/10665/254582/1/WER9206.pdf?ua=1>, accessed March
- ¹⁶ Ipsen J.: Circulating antitoxin at the onset of diphtheria in 425 patients. *J Immunol*. 54:325-347 1946
- ¹⁷ Björkholm B., Böttiger M., Christensen B., et al.: Antitoxin antibody levels and the outcome of illness during an outbreak of diphtheria among alcoholics. *Scand J Infect Dis*. 18:235-239 1986
- ¹⁸ Danilova E., Jenum P.A., Skogen V., et al.: Antidiphtheria antibody responses in patients and carriers of *Corynebacterium diphtheriae* in the Arkangelsk region of Russia. *Clin Vaccine Immunol*. 13:627-632 2006
- ¹⁹ Ohuabunwo C., Perevoscikovs J., Griskevica A., et al.: Respiratory diphtheria among highly vaccinated military trainees in Latvia: improved protection from DT compared with Td booster vaccination. *Scand J Infect Dis*. 37:813-820 2005
- ²⁰ Efstratiou A., Maple P.A.C.: Laboratory Diagnosis of Diphtheria. 1994 World Health Organization Copenhagen Expanded Programme on Immunization in the European Region
- ²¹ The Immunological Basis for Immunization Series Module 2: Diphtheria Update 2009.
http://apps.who.int/iris/bitstream/10665/44094/1/9789241597869_eng.pdf, accessed Jan 2017
- ²² Hasselhorn, HM, Nübling M, Tiller FW, Hofmann F. Factors influencing immunity against diphtheria in adults. *Vaccine*, Vol. 16, No. 1, pp. 70–75, 1998.
- ²³ Galazka A.M., Robertson S.E.: Immunization against diphtheria with special emphasis on immunization of adults.
- ²⁴ Golaz A., Hardy I.B., Glushkevich T.G., et al.: Evaluation of a single dose of diphtheria-tetanus toxoids among adults in Odessa, Ukraine, 1995: immunogenicity and adverse reactions. *J Infect Dis*. 181 (Suppl. 1):S203-S207 2000
- ²⁵ Sutter R.W., Hardy I.R., Kozlova I.A., et al.: Immunogenicity of tetanus-diphtheria toxoids (Td) among Ukrainian adults: implications for diphtheria control in the newly independent states of the former Soviet Union. *J Infect Dis*. 181 (Suppl. 1):S197-S202 2000
- ²⁶ Rønne T., Valentelis R., Tarum S., et al.: Immune response to diphtheria booster vaccine in the Baltic States. *J Infect Dis*. 181 (Suppl. 1):S213-S219 2000

-
- ²⁷ Khetsuriani N., Music S., Deforest A., et al.: Evaluation of a single dose of diphtheria toxoid among adults in the Republic of Georgia, 1995: immunogenicity and adverse reactions. *J Infect Dis*.
- ²⁸ Di Giovine, P., Kafatos, G., Nardone, A., Andrews, N., Ölander, R. M., Alfarone, G., ... & O'flanagan, D. (2013). Comparative seroepidemiology of diphtheria in six European countries and Israel. *Epidemiology and infection*, 141(01), 132-142.
- ²⁹ Mossong, J., Putz, L., SHKEDY, Z., & Schneider, F. (2006). Seroepidemiology of diphtheria and pertussis in Luxembourg in 2000. *Epidemiology and infection*, 134(03), 573-578.
- ³⁰ Ang LW, James L, Goh KT. Prevalence of diphtheria and tetanus antibodies among adults in Singapore: a national serological study to identify most susceptible population groups. *Journal of Public Health | Vol. 38, No. 1*, pp. 99–105
- ³¹ Xiaomei Li, Meng Chen, Tiegang Zhang, Juan Li, Yang Zeng, and Li Lu. Seroepidemiology of diphtheria and pertussis in Beijing, China: A cross-sectional study. *Human Vaccines & Immunotherapeutics* 11:10, 2434--2439; October 2015.
- ³² Sein C, Tiwari T, Macneil A, Wannemuehler K, Soulaphy C, Souliphone P, Reyburn R, Ramirez Gonzalez A, Watkins M, Goodson JL. Diphtheria outbreak in Lao People's Democratic Republic, 2012-2013. *Vaccine*. 2016 Aug 5;34(36):4321-6.
- ³³ Das PP, Patgiri SJ, Saikia L, Paul D. Recent Outbreaks of Diphtheria in Dibrugarh District, Assam, India. *J Clin Diagn Res*. 2016 Jul;10(7):DR01-3.
- ³⁴ ECDC Annual Epidemiology Report. <http://ecdc.europa.eu/en/healthtopics/diphtheria/Pages/Annual-epidemiological-report-2016.aspx>, accessed March 2017.
- ³⁵ Bisgard et al. Diphtheria Toxoid Vaccine Effectiveness: A Case-Control Study in Russia. *The Journal of Infectious Diseases* 2000;181(Suppl 1):S184–7.
- ³⁶ Brennan et al. How Many Doses of Diphtheria Toxoid Are Required for Protection in Adults? Results of a Case-Control Study among 40- to 49-Year-Old Adults in the Russian Federation. *The Journal of Infectious Diseases* 2000;181(Suppl 1):S193–6.
- ³⁷ Chen. Et al. Ukraine, 1992: First Assessment of Diphtheria Vaccine Effectiveness during the Recent Resurgence of Diphtheria in the Former Soviet Union. *The Journal of Infectious Diseases* 2000;181(Suppl 1):S178–83
- ³⁸ Murakami et al. Endemic diphtheria in Ho Chi Minh City; Viet Nam: A matched case-control study to identify risk factors of incidence. *Vaccine* 28 (2010) 8141–8146.
- ³⁹ Tsu et al. Case-Control Evaluation of an Adult Diphtheria Immunization Program in Ukraine. *The Journal of Infectious Diseases* 2000;181(Suppl 1):S188–92.
- ⁴⁰ Rakhmanova et al. Diphtheria Outbreak in St. Petersburg: Clinical Characteristics of 1,860 Adult Patients. *Scand J Infect Dis* 28: 37–40, 1996.
- ⁴¹ Jones et al. Diphtheria: a possible foodborne outbreak in Hodeida, Yemen Arab Republic. *Bulletin of the World Health Organization*, 63 (2): 287-293 (1985).
- ⁴² Vitek et al. Risk of diphtheria among schoolchildren in the Russian Federation in relation to time since last vaccination. *Lancet* 1999; 353: 355–58.
- ⁴³ Amanna et al. Duration of Humoral Immunity to Common Viral and Vaccine Antigens. *N Engl J Med* 2007;357:1903-15.
- ⁴⁴ Goncalves et al. Levels of diphtheria and tetanus specific IgG of Portuguese adult women, before and after vaccination with adult type Td. Duration of immunity following vaccination. *BMC Public Health* 2007, 7:109
- ⁴⁵ Grasse et al. Booster vaccination against tetanus and diphtheria: insufficient protection against diphtheria in young and elderly adults. *Grasse et al. Immunity & Ageing* (2016) 13:26
- ⁴⁶ Hainz et al.[Vaccine protection in the elderly: are Austrian seniors adequately protected by vaccinations?]. *Wien Klin. Wochenschrift* 2002, 114/5-6: 187-193
- ⁴⁷ Kaml et al. Booster vaccination in the elderly: Their success depends on the vaccine type applied earlier in life as well as on pre-vaccination antibody titers. *Vaccine* 24 (2006) 6808–6811
- ⁴⁸ Swart et al. Long-Term Protection against Diphtheria in the Netherlands after 50 Years of Vaccination: Results from a Seroepidemiological Study. *PLoS ONE* 11(2): e0148605.
- ⁴⁹ Tomovici et al. Humoral immunity 10 years after booster immunization with an adolescent and adult formulation combined tetanus, diphtheria, and 5-component acellular pertussis vaccine. *Vaccine* 30 (2012) 2647–2653.

⁵⁰ Vandermeulen et al Decennial administration in young adults of a reduced-antigen content diphtheria, tetanus, acellular pertussis vaccine containing two different concentrations of aluminium. *Vaccine* 33 (2015) 3026–3034

⁵¹ Weinberger et al Recall Responses to Tetanus and Diphtheria Vaccination Are Frequently Insufficient in Elderly Persons 2013 *PlosONE*. *PLoS ONE* 8(12): e82967.

⁵² Hammarlund et al Durability of Vaccine-Induced Immunity Against Tetanus and Diphtheria Toxins: A Cross-sectional Analysis. *Clinical Infectious Diseases*. 2016;62(9):1111–8

⁵³ Völzke et al Susceptibility to diphtheria in adults: prevalence and relationship to gender and social variables. *Clin Microbiol Infect* 2006; 12: 961–967

⁵⁴ Amanna IJ, Carlson NE, Slifka MK. Duration of humoral immunity to common viral and vaccine antigens. *N Engl J Med* 2007; 357:1903–15.

⁵⁵ Schurink-van 't Klooster TM, Melker HE (2015) The National Immunisation Programme in the Netherlands. Surveillance and developments in 2014–2015. Bilthoven: National Institute for Public Health and the Environment [in Dutch: RIVM] RIVM Report 2015–0134 RIVM Report 2015–0134.

⁵⁶ Health Council of the Netherlands (2004) Vaccination against pertussis. The Hague: Health Council of the Netherlands.

Diphtheria anti-toxin (DAT) supply issues: brief review and proposition

Diphtheria anti-toxin (DAT) was the first immunotherapeutic ever used. It was developed in the late 19th century, and until the development and use of diphtheria vaccine, DAT was the primary intervention for diphtheria, reducing case fatality rates from 25-50% in untreated patients to 3% in patients treated earlyⁱ. It is obtained by immunizing horses with inactivated diphtheria toxin, and purifying the immunoglobulins.

During the first half of the 20th century many countries produced DAT for national use, however with the increasing use of vaccine and declining incidence of the disease the market for DAT collapsed, and with it the number of manufacturers. As a result there is no manufacturer producing DAT on a routine basis, and only a few manufacturers have retained the procedures and necessary horse flocks to be able to provide this product (see below).

A few countries have been maintaining stockpiles, however these stockpiles are small and most have either expired or have had the expiry dates extended through re-testing by an independent laboratory to confirm activity of the product. In Europe 60% of member states have reported obtaining DAT supplies even for diagnostics highlighting risksⁱⁱ. Other countries such as South Africa facing small outbreaks, have made requests to manufacturers for supply of a few vials. Effective treatment of cases requires rapid access to and administration of DAT. In the event of a suspected or confirmed case in the absence of a stockpile the time taken to identify a manufacturer with remaining supply within expiry date (if at all available), and the time to arrange for shipment, may mean the supply arrives too late to save the lives of the patients. Regional stockpiles that can be readily accessed may be a preferable solution.

Alternatives to equine-derived DAT:

Human polyclonal DAT is available for diagnostic purposes. While a DAT prepared from blood donations was developed in Australia in the 1970sⁱⁱⁱ there is currently no supply for therapeutic use. Studies during the outbreak in Russia in the 1990s showed that plasma from selected donors amongst convalescent patients could be used^{iv} however this is not a commercial product.

Several groups are developing monoclonal DAT preparations^v including MassBio (USA) which has demonstrated efficacy of their monoclonal in preclinical models. A monoclonal DAT preparation could have significant advantages over equine DAT in that the quality and safety issues associated with equine preparations would be avoided, and in theory supplies could be assured. It will however require several years of clinical development and several million dollars of public-sector funds to bring this product to approval, and the production costs are unlikely to be less than for the equine product. While this may become a useful product in the future it is not currently available.

Manufacturing capacity for equine DAT:

The manufacturers known (through written confirmation) to have current DAT manufacturing capacity (but not necessarily maintaining supplies) are:

India: VINS Bioproducts Ltd.

Premium serums & vaccines Ltd. (which has acquired the SILL process) .

Brazil: Butantan Institute.

Manufacturers thought to have DAT manufacturing capacity (no reply to written enquiry to date):

Russia: Microgen

Japan: Kaketsuken

Iran: Razi Institute

Potential Needs

The number of reported cases each year and by region are as follows:

Region	2011	2012	2013	2014	2015
AFR	13	27	128	1	1654
AMR	12	2	5	10	49
EMR	352	334	392	40	43
EUR	33	32	33	35	54
SEAR	5179	3953	4080	7666	2504
WPR	37	142	42	22	226

This suggests that an **annual supply of 4000-8000 treatment courses** would be required to enable access for all patients. DAT is administered intravenously in a saline drip over 2-4 hours. Testing for sensitivity to DAT through a scratch test or an ID test must be performed prior to administering DAT. Treatment therefore requires access to appropriate health care infrastructure as well as appropriate diagnostic capacity.

DAT is usually provided as lyophilised immunoglobulin preparation containing 10,000 IU per vial, and treatment requires between 10,000 (for early pharyngeal disease) and 100,000 IU for systemic disease or in patients with diffuse swelling of the neck^{vi}. Assuming an average requirement of 40,000 IU, 8000 treatment courses therefore corresponds to roughly 32000 vials.

Initial discussions suggest that at such a scale the price per vial will be less than \$10 per vial.

Conclusion:

The existing small stockpiles are either depleted or running out, and are largely insufficient to meet the potential needs in low- and middle- income countries. The establishment and maintenance of larger stockpiles is very feasible and several companies are capable of generating sufficient product. However, in order for such a stockpile to be procured by UN agencies prequalification will be required, and to date no equine polyclonal serum has been prequalified. The recent approach to provide an emergency listing for equine-derived anti-snake venom preparations may provide a mechanism for such procurement.

The potential size of such a stockpile needs careful consideration since treatment of diphtheria cases is also dependent on diagnostic capacity and provision of health care services.

ⁱ Naiditch MJ, Bower AG. Diphtheria. A study of 1433 cases observed during a ten year period at the Los Angeles County Hospital. *Am J Med.* 1954;17:229-45

ⁱⁱ ECDC technical Report: Gap analysis on securing diphtheria diagnostic capacity in the EU/EEA. Oct 2016.

ⁱⁱⁱ Hartman LJ. Bioavailability study of diphtheria immunoglobulin (human). *Pathology* 1979. 11(3) 385-7.

^{iv} Bissumbhar B, Rakhmanova AG, Berbers GA, Iakolev A, Nosikova E, Melnick O, et al. Evaluation of diphtheria convalescent patients to serve as donors for the production of anti-diphtheria immunoglobulin preparations. *Vaccine.* 2004;22(15-16):1886-91. <http://dx.doi.org/10.1016/j.vaccine.2003>

^v Huygen K. Development of human monoclonal antibodies to diphtheria toxin: a solution for the increasing lack of equine DAT for therapeutic use? *Virulence*, 2016. 6, 613-5.

^{vi} <https://www.cdc.gov/diphtheria/downloads/protocol.pdf>