World Health Organization

Department of Immunization, Vaccines and Biologicals (IVB)

SAGE

April 2015

Strategic Advisory Group of Experts on Immunization
14-16 April 2015

Executive Boardroom
WHO HQ, Geneva

World Health Organization

SAGE April 2015

This booklet contains key background documents for the meeting of the
Strategic Advisory Group of Experts (SAGE) on immunization
14-16 April 2015

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

http://apps.who.int/immunization/sage/meetings/2015/april/en/

For password, please send an e-mail to: *sageexecsec@who.int*

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Version: 25 March 2015

World Health Organization

Draft Agenda
Meeting of the Strategic Advisory Group of Experts on Immunization (SAGE)
14 – 16 April 2015
EB Room, WHO, HQ, Geneva

Tuesday, 14 April 2015

Time	Session	Purpose of session, target outcomes and questions for SAGE	
9:00	**Welcome – introduction of participants** J. Abramson, 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
10:00	**Coffee/tea break**	**Break**	**30 min.**
10:30	**Report from Director, IVB - Session 1, (Contd.)**		
11:50	**Report from GAVI - Session 2** Report from the GAVI Alliance, S. Berkley, TBC, GAVI Alliance, 30 min. Discussion: 30 min.	**FOR INFORMATION**	1h
12:50	**Lunch**	**Break**	**1h 20 min**
14:10	**Reports from other Advisory Committees on Immunization - Session 3** Report of the Global Advisory Committee on Vaccine Safety (GACVS), M. Wharton, Chair of GACVS, 10 min. Discussion: 10 min. Product Development for Vaccines Advisory Committee (PDVAC) criteria used for prioritizing vaccines for the work of the Initiative for Vaccine Research, D. Kaslow, Chair of PDVAC, 10 min. Discussion: 10 min.	**FOR INFORMATION**	40 min.

14:50	**Coffee/tea break**	**Break**	**30 min.**
15:20	**Global polio eradication initiative - Session 4** Objective of the session; overview of Global Polio Eradication Initiative, H. Jafari, WHO, 15 min. Epidemiology of cVDPVs and updated SIA calendar, A, Quddus, WHO, 10 min. Report from SAGE WG (1. Contingency plan in case of prolonged cVDPV circulation and 2. WHO verification process of essential facilities), P. Figueroa, Chair of the Polio Working Group, 20 min. Discussion: 45 min. Updates on preparation for OPV2 withdrawal (e.g. IPV introduction, operationalizing OPV2 withdrawal, bOPV licensures and containment), M. Zaffran, WHO, 20 min. Discussion: 40 min.	**FOR DISCUSSION AND DECISION** **For decision** • Review/endorse the contingency plans if persistent cVDPV2 continue to circulate • Review/endorse the proposed process for WHO to verify that essential poliovirus facilities certified by national authorities comply with GAP III **For information** • Review updated SIA calendar • Review updates on preparation for OPV2 withdrawal (e.g. Implementation support for tOPV-bOPV switch in OPV2 withdrawal) and bOPV licensure	2h 30 min.
17:50	**Cocktail**		

Wednesday, 15 April 2015

08:30	**Administration of multiple injectable vaccines - Session 5** Introduction, K. O'Brien , SAGE Member, 10 min. Acceptability of 3 vaccine injections given to infants in South Africa, C. Wiysonge, University of Stellenbosch, 10 min. Summary of evidence on the administration of multiple injectable vaccines in infants: attitudes of healthcare providers and caregivers, A. Wallace, US CDC, 10 min. Summary of evidence on immune system effects, safety, administration practices and programmatic issues related to administration of multiple injectable vaccines during a single visit, S. Dolan, US CDC, 20 min. Summary of the findings and proposed recommendations, K. O'Brien, SAGE Member, 10 min. Discussion: 1h	**FOR DISCUSSION** SAGE recommendations on administration of multiple injectable vaccines to infants in a single visit.	2h
10:30	**Coffee/tea break**	**Break**	**30 min.**
11:00	**Reducing pain and distress at the time of vaccination - Session 6** Introduction (importance, landscape analysis, objectives, and methods), N. Turner, SAGE member, 15 min. Impact of pain and distress at the time of vaccination N. MacDonald, Dalhousie University, Halifax, 10 min. Systematic review of effectiveness and safety of interventions aimed at reducing pain and distress at the time of vaccination, A. Taddio, The Hospital for Sick Children, Toronto, 15 min. Proposed recommendations for reducing pain and distress at the time of vaccination, N. Turner, SAGE member, 20 min. Discussion: 1h	**FOR DECISION** Recommendations on potential interventions to reduce pain and distress at the time of vaccination	2h
13:00	**Lunch**	**Break**	**1h**

14:00	**Sustainable Access to Vaccines in Middle Income Countries: a Shared Strategy - Session 7** Introduction of the session, Y. Al-Mazrou, SAGE Member, 5 min. The 'Middle Income Countries issue': reframing the problem. J. Andrus, Sabin Vaccine Institute, 15 min. A shared MICs strategy. T. Cernuschi, WHO and G. Gandhi, UNICEF, 20 min. Discussion: 80 min.	**FOR INFORMATION AND DISCUSSION** • SAGE will be presented with the output of the MICs task force and the specific areas of the proposed comprehensive strategy and its related priority activities • SAGE will be requested to indicate its concurrence with the general directions of the proposed MICs strategy and to provide any related suggestions for adjustment	2h
16:00	**Coffee/tea break**		**30 min.**
16:30	**Ebola vaccine and vaccination - Session 8** Introduction, O. Tomori, Co-chair of the SAGE working group on Ebola vaccines, 5 min. Update on the epidemiology of EVD, C. Dye, WHO, 10 min. Status of phase 1 and 2 trials and summary of preliminary results from phase 1 trials, V. Sathiyamoorthy, WHO, 15 min. Update on phase 3 trials (design and status), A.-M. Henao Restrepo, WHO, 10 min. Preparations for vaccine deployment, M.-P. Preziosi, WHO, 10 min. Framework for recommendations for deployment of vaccines, H. Rees, Co-chair of the SAGE working group on Ebola vaccines WG Co-chair, 10 min. Discussion: 1h	**FOR INFORMATION AND DISCUSSION** • Provide SAGE with an update on the status of the current epidemic, vaccine clinical trials and an update on the process and scope of the recommendations that will be made by the WG and the preparatory work for deployment. • Get input on the scope and framework of the WG for the issuance of recommendations on the deployment of vaccines	2h
18:30	**End of day**		

Thursday, 16 April 2015

08:30	**Maternal vaccination - Session 9** Introduction, C.-A. Siegrist, SAGE member, 5 min. WHO's agenda on Maternal Immunization – an update, J. Hombach, WHO, 10 min. Review of influenza disease risk and incidence relevant to maternal immunization: Report from WHO IVIR-AC influenza working group, B. Gessner, Agence de Médecine Préventive, 15 min. Discussion: 10 min. Summary of the March maternal influenza meeting on new data and implementation, K. O'Brien, SAGE Member, 20 min. Discussion: 10 min. Implementation research gaps for furthering maternal immunization, J. Ortiz, WHO, 10 min. Discussion. 40 min.	**FOR INFORMATION AND DISCUSSION** • Update SAGE on the latest data , activities and achievements with respect to maternal immunization • Solicit SAGE's input on the strategic directions for implementation research in support of maternal immunization	2h
10:30	**Coffee/tea break**	**Break**	**30 min.**
11:00	**Pertussis vaccination schedules - Session 10** Introduction: Background and framing of the questions for SAGE, C.-A. Siegrist, Chair of the SAGE Pertussis Working Group, 10 min. Evidence in support/against various primary DTP vaccination schedules, E. Miller, Member of the SAGE Pertussis Working Group, 20 min. Modeling of impact of different DTP schedules. A. Clark, LSHTM, 15 min. Summary of evidence, E. Miller, Member of the SAGE Pertussis Working Group, 10 min Recommendations, C.-A. Siegrist, Chair of the SAGE Pertussis Working Group, 10 min. Discussion: 1h 15 min.	**FOR DECISION** With primary focus on pertussis, review the evidence in support/against different schedules for DTP containing vaccines and the impact of different vaccination strategies. Update recommendations on the optimal schedules for DTP containing vaccines with a view to lead to the updating of the pertussis position paper.	2h 30 min.
13:30	**Closing**		20 min.
13:50	**End of meeting**		

Meeting of the WHO Strategic Advisory Group of Experts (SAGE) on Immunization
14-16 April 2015
Geneva, Switzerland

SAGE members

Professor Jon S. Abramson (Chair) Department of Pediatrics **Wake Forest University Baptist Medical Centre** Medical Center Blvd Winston-Salem 27157 NC **United States of America**
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Professor Narendra Kumar Arora (Vice-Chair) Executive Director **The INCLEN Trust International** Second Floor, F-1/5 Okhla Industrial Area Phase 1 New Delhi 110020 **India**
Professor Zulfiqar Ahmed Bhutta Co-Director, Robert Harding Chair in Global Child Health and Policy **The Hospital for Sick Children** **University of Toronto** 686 Bay Street Toronto M5G 404 Ontario **Canada**
Professor Juhani Eskola Director General, THL Health Protection **National Institute for Health and Welfare** Mannerheimintie 166 P.O. Box 30 00271 Helsinki **Finland**
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Professor J. Peter Figueroa Public Health, Epidemiology & AIDS, Department of Community Health & Psychiatry Faculty of Medical Sciences **University of the West Indies** Gilbraltar Camp Road Mona, Kingston 7 **Jamaica**

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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 policies and strategies, ranging from vaccines and technology, research and development, to delivery of immunization and its linkages with other health interventions. SAGE is concerned not just with childhood vaccines and immunization, but all vaccine-preventable diseases.

SAGE advises the WHO Director-General specifically on the:

1. adequacy of progress towards the achievement of the goals of the Decade of Vaccines (DoV) Collaboration and Global Vaccine Action Plan (GVAP);
2. major issues and challenges to be addressed with respect to achieving the goals of the DoV and GVAP;
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 to achieve the DoV and GVAP goals consistent with its mandate and considering the comparative advantages and the respective roles of partner organizations;
6. cross-departmental activities and initiatives related to vaccine and immunization technologies and strategies and linkages with other health interventions;
7. engagement of WHO in partnerships that will enhance achievement of global immunization goals.

Membership

The SAGE comprises 15 members, who shall serve in their personal capacity and represent a broad range of disciplines encompassing many aspects of immunization and vaccines.

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., influenza control, diarrhoeal diseases, respiratory diseases, research, biologics, immunization safety); and
3. the three major strategic areas of WHO's work relating to immunization (i.e., accelerating innovation, ensuring quality and safety, and maximizing access and links with other health interventions).

SAGE members, including the Chairperson, shall be nominated by the WHO IVB Director in consultation with WHO Regional Offices and other relevant WHO departments 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.

SAGE members are appointed by the WHO Director-General; all nominations for new SAGE members, as well as renewals and discontinuation of appointments to SAGE, must be approved by the WHO Director-General. Consideration will be given to ensuring appropriate geographic representation and gender balance.

Members of SAGE shall be appointed to serve for an initial term of three years. Such three-year terms 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 Chairmanship.

Prior to being appointed as SAGE members and prior to renewal of term, nominees and current SAGE members shall be required to complete a WHO Declaration of Interests as per the attached form (Annex 1).

In addition, prior to confirmation by WHO of their appointment as SAGE members, SAGE nominees shall be required to sign a Confidentiality Undertaking (Annex 2). 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.

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

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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; and
(3) a lack of professionalism involving, for example, a breach of confidentiality.

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 this 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. Focused technical input will be solicited from identified experts and advisory scientific groups.

The Committee has no executive or regulatory function. Its role is solely to provide advice and recommendations to the Director-General of WHO, and includes providing advice and recommendations on urgent matters 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.

Meetings and operational procedures

SAGE will normally meet biannually. The frequency of meetings may, however, be adjusted as necessary. Decisions or recommendations will, as a rule, be taken by consensus.

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 along with the meeting documentation on the SAGE website after the meeting.

UNICEF, the Secretariat of the Global Alliance for Vaccines and Immunization (GAVI), and WHO Regional Offices will participate as observers in SAGE meetings and deliberations.

WHO may also invite other observers to SAGE meetings, including representatives from WHO regional technical advisory groups, non-governmental organizations (NGO), international professional organizations, technical agencies, donor organizations and associations of manufacturers of vaccines and immunization technologies.

Additional experts may be invited to meetings, as appropriate, to further contribute to specific agenda items.

SAGE will work with WHO to develop its priorities of work and meeting agendas.

SAGE will be kept informed by WHO and partner agencies of progress in implementation of strategies and the attainment of objectives at country and regional level. SAGE will also be informed of policies and recommendations set by the WHO regional technical advisory groups. WHO, with advice from SAGE, will determine which policy recommendation issues and information from other WHO technical advisory groups should be brought to the attention of SAGE.

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 the full SAGE in an open public forum. These Working Groups are established on a time-limited basis to help address specific questions identified by SAGE when the issue is particularly complicated and could not be addressed by an existing standing WHO advisory committees. 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.

In addition to attendance of meetings, 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 departmental or cross-departmental meetings.

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 reports to the WHO Director-General (or designee(s)). The SAGE Chairperson will debrief the Director-General (or designee) and the IVB Director following each SAGE meeting. Minutes of SAGE meetings will be taken and circulated among SAGE members. The recommendations/conclusions of SAGE meeting shall be published, with the prior approval of WHO, in the Weekly Epidemiological Record and posted on the IVB Departmental website within two months of each SAGE meeting. In addition, these recommendations and conclusions will be translated into all the WHO headquarters official languages and posted on the IVB Departmental website.

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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 the full SAGE in an open public forum.

These Working Groups are 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.

The need for and creation of a Working Group is discussed and agreed during SAGE meetings or SAGE preparatory teleconferences.

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 need to be 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, the Chair of the Working Group, 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 SAGE members (one of whom functions as Chair), WHO staff (one of whom functions as the Working Group technical lead), and additional subject matter experts serving in their own individual capacity and with a view to meet the identified needed expertise for the group. This may include organizations representatives, and members of regional technical consultative groups. 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.

The size of the Working Group should not exceed 10 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 reference of the Working Group and indication of the desirable expertise. SAGE members, regional offices, 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 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 also identify other names and rationale for proposed selection. In addition to meeting the required expertise, attention will be given to ensure proper diversity in the Group.

Working Group Process
WHO staff 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 research questions developed by the Working Group in order to propose appropriate vaccine policy decisions.

SAGE Working Groups are not allowed to render consensus advice or recommendations directly to the WHO D-G. 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 the SAGE can deliberate and act. Thus, while SAGE Working Groups can and should examine an area in detail and define the issues, including development of options for recommendations, the actual processes of group deliberation resulting in development of the group's consensus and final recommendations must occur in the public forum of SAGE meetings.

Effective communication and a strong working collaboration between the Working Group Chair the 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 shortly after the meetings. Once the minutes are approved by the Working Group, they are circulated to SAGE members. 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 except 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.

In-person meetings of Working Groups may facilitate progress. If possible, they should be anticipated at least two months in advance of the SAGE meeting.

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 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.

Management of Conflict of Interest
The value and impact of SAGE recommendations and WHO policies and 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. Members are expected to inform WHO on any change in relevant interests.

World Health Organization

CURRENT SAGE WORKING GROUPS

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

- Peter Figueroa (Chair of Working Group), University of the West Indies, Jamaica
- Hyam Bashour, changed as of February 2013- retired from Damascus University, Syria (SAGE member until April 2011)
- Zulfiqar Bhutta, The Aga Khan University, Pakistan (Joined the Working Group in March 2012)
- Elizabeth Miller (SAGE member and Chair of the Working Group until February 2014), Health Protection Agency, United Kingdom
- Yagob Al-Mazrou, Secretary General - Health Services Council of the Kingdom of Saudi Arabia, Saudi Arabia (Joined the group in February 2015).

Experts

- Walter Dowdle, Task Force for Child Health, USA
- Nick Grassly, Imperial College, UK
- Jacob John, Christian Medical College, India
- Antoine Kabore, retired (formally of WHO/AFRO), Burkina Faso
- Francis Nkrumah, retired (formally of Noguchi Memorial Institute for Medical Research, University of Ghana Medical School, Ghana)
- Walter Orenstein, Emory University, USA
- Kimberley Thompson, Kids Risk Project, Harvard School of Public Health, USA

2. Joint technical expert group (JTEG) on malaria vaccines entering pivotal phase 3 trials & beyond (established April 2009)

JTEG acts as a SAGE (Strategic Advisory Group of Experts on Immunization) Working Group and also as a MPAC (Malaria Policy Advisory Committee) Technical Expert Group. The constitution of JTEG took into account both SAGE and MPAC considerations. The Chair, Peter Smith, is neither a SAGE nor MPAC member. Peter Smith was chosen as an expert in both immunization and malaria policy, having also served as Chair of other immunization and malaria-related WHO advisory committees.

Terms of reference

JTEG provides advice to SAGE and MPAC on activities related to the development of malaria vaccines at or nearing the pivotal phase 3 trial stage. The specific responsibilities of the group are to provide recommendations on:

- The clinical trial data necessary and desirable for evaluation of the public health impact of a malaria vaccine in malaria endemic countries
- The design, conduct, analyses and interpretation of Phase 2, Phase 3 and Phase 4 trials of malaria vaccines.
- The duration and nature of follow-up of participants in planned Phase 3 trials of malaria vaccines.
- The minimum safety and efficacy data to be collected in clinical trials, and data on any impact of malaria vaccines on the immunogenicity of other vaccines, to enable evaluation by WHO for policy recommendations.
- The evaluation of immunogenicity of malaria vaccines in Phase 3 trials and beyond, in particular with regard to possible development of surrogate markers for efficacy.

Composition

SAGE Members

- Zulfiqar Bhutta, Aga Khan University, Pakistan
- Claire-Anne Siegrist, University of Geneva, Switzerland
- Fred Were, Executive Director - Professor, Department of Paediatrics and Child Health, University of Nairobi, Kenya

Experts

- Peter Smith, Chair, London School of Hygiene and Tropical Medicine, UK
- Fred Binka, University of Ghana, Ghana
- Kalifa Bojang, MRC Laboratories, The Gambia
- Blaise Genton, University of Lausanne, Switzerland
- Robert Johnson,National Institutes of Allergy and Infectious Disease, USA
- Kamini Mendis, Independent Consultant, Colombo, Sri Lanka
- Paul Milligan, London School of Hygiene and Tropical Medicine, UK
- Malcolm Molyneux, University of Malawi, Malawi
- Mahamadou Thera, University of Bamako, Mali
- Janet Wittes, Statistics Collaborative Inc., USA

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

Terms of Reference

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

Composition

SAGE Members

- Narendra Arora, International Clinical Epidemiology Network, India

- El Tayeb Ahmed El Sayed, Federal Ministry of Health, Sudan (SAGE member until June 2012)
- David Durrheim, Hunter New England Area Health Service and Professor of Public Health, Australia (SAGE member until April 2012)
- Peter Figueroa, Chair of Working Group. University of the West Indies, Jamaica
- Helen Rees, University of Witwatersrand, South Africa (SAGE member until August 2013)

Experts

- Hyam Bashour, Department of Family and Community Medicine, Damascus University, Syria (SAGE member until April 2011)
- Natasha Crowcroft, Surveillance and Epidemiology, Public Health Ontario, Canada
- Heidi Larson, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, UK (Until March 2015)
- Pier Luigi Lopalco, European Centre for Disease Prevention and Control, Sweden
- William Moss, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
- Susan Reef, Global Immunization Division, Centers for Disease Control and Prevention, USA
- Makoto Takeda, Department of Virology 3, National Institute of Infectious Diseases, Japan

4. SAGE Working Group on Pertussis vaccines (established – March 2013)

Terms of Reference

In light of the recent resurgence of pertussis in some industrialized countries with their toll in terms of infant deaths it was agreed between SAGE and WHO that a new working group (on pertussis would be established to prepare for a SAGE review of the data and to consider updating current pertussis vaccine recommendations as published in the 2010 pertussis vaccine position paper. This is also an opportunity for SAGE to review new data on the effectiveness of various vaccination strategies aimed at reducing infant mortality as well as the pertussis related outcome of the Vaccine schedule optimization project.

Specifically the working group will be asked to:

- Review epidemiological data from countries that have or not experienced a resurgence of pertussis, in particular data that relates to the quality and duration of protection of protection for wP and aP vaccines
- Review, in the context of the above, accumulated data on the usefulness of the following strategies to prevent early mortality
    - Role of vaccination of adolescents and adults
    - "Cocooning"
    - Vaccination of pregnant and lactating mothers
    - Vaccination of newborns

- Update estimates of effectiveness of 1 or 2 dose schedules against mortality
- Create optimal primary vaccination schedule and timing of booster dose(s)
- Propose, based on the above and as necessary, an update of the current recommendations on the use of wP/aP vaccine.

Composition

SAGE Members

- Claire-Anne Siegrist, Chair of Working Group, Department of Pediatrics, University of Geneva, Switzerland
- Elizabeth Miller, (SAGE member and Chair of the Working Group until February 2014) , Public Health England, UK
- Piyanit Tharmaphornpilas, National Immunization Program, Ministry of Public Health, Nonthaburi, Thailand

Experts

- Tom Clark, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, USA
- Kathryn Edwards, Vanderbilt Vaccine Research Program, Vanderbilt University School of Medicine, Nashville, USA
- Nicole Guiso, Institut Pasteur Research Unit, Institut Pasteur, Paris, France
- Scott A. Halperin, Canadian Center for Vaccinology, Dalhousie University, Halifax, Canada
- Teeranart Jivapaisarnpong, Institute of Biological Products, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand

- Daniel Levy-Bruhl, Infectious Diseases Department, Institut de Veille Sanitaire, Saint-Maurice, France
- Peter McIntyre, National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, Sydney, Australia
- Gabriela Moreno, Departments of Epidemiology and Immunizations, Ministry of Health, Santiago, Chile
- Carl Heinz Wirsing von König, National reference laboratory for Bordetella infections, Krefeld, Germany

5. 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:

- 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;
- 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;
- identify successes, challenges and areas where additional efforts or corrective actions by countries, regions, partners, donor agencies or other parties, are needed;
- identify and document best practices;
- prepare the GVAP implementation annual report to be presented to the SAGE, and thereafter, with SAGE inputs, be submitted for discussion to the WHO January EB meeting, to the WHA and the independent Expert Review Group (iERG) for the UN Secretary General's Global Strategy for Women's and Children's Health.

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

Composition

SAGE Members

- Narendra Arora, Chair of the Working Group, Executive director, International Clinical Epidemiology Network, India
- Yagob Al-Mazrou, Secretary General - Health Services Council of the Kingdom of Saudi Arabia, Saudi Arabia
- Helen Rees, Executive Director - Reproductive Health Research Unit, University of Witwatersrand, South Africa (SAGE member until April 2013)

Experts

- Alejandro Cravioto, Chief Scientific Officer, International Vaccine Institute, Seoul, Republic of Korea
- Fuqiang Cui, Epidemiology Professor, Deputy Director National Immunization Program, China CDC, China
- Elizabeth Ferdinand, Senior Medical Officer of Health and Barbados EPI Manager, Barbados
- Shawn Gilchrist, President, S. Gilchrist Consulting Services Inc., Canada (resigned from the Working Group May 2014 for personal reasons and replaced by Yvette Madrid)
- Alan Hinman, Senior Public Health Scientist - Task Force for Global Health, USA
- Stephen Inglis, Director, National Institute Biological Standards & Control, Health Protection Agency, UK
- Yvette Madrid, PATH, Switzerland
- Amani Mahmoud Mustafa, EPI Ministry of Health, Sudan
- Rebecca Martin, Director Global Immunization Division, US CDC, USA
- Rozina Mistry, Lecturer and Course Director, Aga Kahn University, Pakistan
- David Salisbury, Director Immunization, Department of Health, UK

6. 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:

- Reviewing the essential evidence required for making policy recommendations and on strategies for deployment of vaccines.
- Reviewing the available epidemiological data to define the risk of disease and mortality in different population groups in order to allow prioritization of vaccination.
- 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.
- Reviewing the data on the projected impact of different vaccination strategies generated by mathematical models.
- Reviewing the synthesis of the above data for presentation to SAGE and in drafting recommendations for consideration by SAGE.
- Reviewing the projections of vaccine supply to inform recommendations on the deployment of vaccines.

Composition

SAGE Members

- Tomori, Oyewale (Co-Chair); Professor of Virology, Redeemer's University, Nigeria
- O'Brien, Kate; Professor, Department of International Health & Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, USA
- Were, Fred; Executive Director - Professor, Department of Paediatrics and Child Health, University of Nairobi, Kenya

Experts

- Rees, Helen (Co-Chair, Chair of the African Task Force on Immunization (TFI)); Executive Director - Reproductive Health Research Unit, University of Witwatersrand, South Africa
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- Ndack, Diop: Lecturer in Socio-Anthropology & Methodology of research in social science. University Cheikh Anta Diop, Dakar, Senegal
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- Wiysonge, Charles (Member of TFI); Professor in Community Health Stellenbosch University; Deputy Director Centre for Evidence-based Heath Care Stellenbosch University, South Africa

Ex-Officio members

- Breiman, Robert; (Chair of WHO Immunization and vaccines related implementation research advisory committee (IVIR-AC))
- Griffiths, Ellwyn; (Chair of WHO Expert Committee on Biological Standardization (ECBS))
- Morgan, Chris; (Chair of WHO Immunization Practices Advisory Committee (IPAC))
- Wharton, Melinda; (Chair of WHO Global Advisory Committee on Vaccine Safety (GACVS))

WHO Secretariat

Focal point: Cherian, Thomas

7. SAGE Working Group on Dengue (established March 2015)

Terms of reference

The Working Group will be asked to review the evidence, identify the information gaps, and formulate proposed recommendations on the use of licensed dengue vaccines for a SAGE review. This review is tentatively scheduled for April 2016. This will lead to the publication of a WHO position paper on the use of dengue vaccines.

- The Working Group will specifically be asked to review data relating to:
- the global prevalence and burden of disease caused by dengue
- the safety, efficacy, and immunogenicity profile of licensed dengue vaccines
- the schedule, age of administration, and potential vaccination strategies for dengue vaccines, including setting-specific attributes that may be important for designing immunization programs
- the disease impact and cost-effectiveness of dengue immunization programs
- identification of key data gaps that may be important for decisions about immunization programs, and recommendations for data collection related to key issues such as long-term safety, duration of protection, etc.
- additional critical issues that need to be considered in drafting proposed recommendations.

Composition

SAGE Members

- Terry Nolan, (Co-Chair of the Working Group), Melbourne School of Population and Global Health, Australia
- Piyanit Tharmaphornpilas, Ministry of Public Health, Thailand

Experts

- Jeremy Farrar, (Co-Chair of the Working Group), Wellcome Trust, UK
- Ananda Amarasinghe, Ministry of Health, Sri Lanka
- Alan Barrett, University of Texas Medical Branch, USA
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- Maria Novaes, Universidade de São Paulo, Brazil
- Lee Ching Ng, National Environment Agency, Singapore
- Amadou Sall, Institut Pasteur de Dakar, Senegal
- Peter Smith, London School of Hygiene and Tropical Medicine, UK
- Wellington Sun, U.S. Food and Drug Administration, USA
- Steve Thomas, Walter Reed Army Institute of Research, USA

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- Joachim Hombach
- Kirsten Vannice

Strategic Advisory Group of Experts (SAGE) on Immunization
14 - 16 April 2015
Executive Boardroom, WHO Headquarters, Geneva, Switzerland

Provisional List of Participants

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Weekly epidemiological record
Relevé épidémiologique hebdomadaire

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Sommaire

Meeting of the Strategic Advisory Group of Experts on immunization, October 2014 – conclusions and recommendations

The Strategic Advisory Group of Experts (SAGE) on immunization[1] met on 21–23 October 2014 in Geneva, Switzerland. This report summarizes the discussions, conclusions and recommendations.[2]

Report from the WHO Department of Immunization, Vaccines and Biologicals

The report focused on: (i) WHO's contribution to the Global Vaccine Action Plan (GVAP) and the process and timelines for developing WHO's vision and mission and prioritizing work on vaccines and immunization from 2015 to 2025 in the context of the GVAP, (ii) regional achievements, challenges, and priorities, (iii) feedback on selected work streams of importance to SAGE including integration, data quality, typhoid conjugate vaccine, maternal immunization, World immunization week, and (iv) SAGE working processes and projected agenda items.

For the future, SAGE requested that WHO give special attention to facilitating greater participation of Civil Society Organizations (CSOs) in immunization activities.

SAGE congratulated the Regions on progress in adapting the GVAP and developing regional vaccine action plans, with regional vaccine action plans already adopted by the European and Western Pacific Regional Committees. The African Region currently faces new challenges due to the Ebola crisis, which adversely affects health programmes, especially in the 3 most heavily Ebola-affected countries

[1] See http://www.who.int/immunization/sage/en/index.html

[2] The complete set of presentations and background materials used for the SAGE meeting of 21–23 October 2014 together with summarized declarations of interests provided by SAGE members are available at http://www.who.int/immunization/sage/meetings/2014/october/en/, accessed in October 2014.

Réunion du Groupe stratégique consultatif d'experts sur la vaccination, octobre 2014 – conclusions et recommandations

Le Groupe stratégique consultatif d'experts (SAGE) sur la vaccination[1] s'est réuni du 21 au 23 octobre 2014 à Genève (Suisse). Le présent rapport résume les discussions, conclusions et recommandations auxquelles il est parvenu.[2]

Rapport du Département OMS Vaccination, vaccins et produits biologiques

Le rapport était axé sur: i) la contribution de l'OMS au Plan d'action mondial pour les vaccins (GVAP), ainsi que sur le processus et les échéances pour élaborer la vision et la mission de l'OMS et pour définir les priorités du travail sur les vaccins et la vaccination de 2015 à 2025 dans le contexte du GVAP; ii) les réalisations, les difficultés et les priorités au niveau régional; iii) le retour d'information sur certains axes de travail importants pour le SAGE, parmi lesquels l'intégration, la qualité des données, le vaccin conjugué contre la typhoïde, la vaccination maternelle, la Semaine mondiale de la vaccination; et iv) les méthodes de travail du SAGE et les points prévus pour discussion dans un bref avenir.

Le SAGE a demandé qu'à l'avenir, l'OMS accorde une attention spéciale aux organisations de la société civile pour faciliter leur plus grande participation aux activités de vaccination.

Le SAGE a félicité les Régions pour les progrès accomplis dans l'adaptation du GVAP et l'élaboration de plans d'action régionaux pour les vaccins, dont deux ont déjà été adoptés par les Comités régionaux de l'Europe et du Pacifique occidental. La Région africaine est actuellement confrontée à de nombreuses difficultés dues à la crise du virus Ebola, qui a des répercussions négatives sur les programmes de santé, en particulier dans les 3 pays les plus

[1] Voir http://www.who.int/immunization/sage/en/index.html

[2] La série complète des communications et des documents de travail de la réunion du SAGE tenue du 21 au 23 octobre 2014, ainsi que les résumés des déclarations d'intérêt fournies par les membres de ce groupe sont disponibles à l'adresse: http://www.who.int/immunization/sage/meetings/2014/october/en/, consulté en octobre 2014.

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where vaccination coverage has dramatically decreased this year. SAGE noted with concern that the Ebola outbreak highlights the vulnerability of the African Region and that steps need to be taken to ensure that progress on immunization is not jeopardized in any future crises. The Region of the Americas recently adopted a resolution to ensure universal health coverage including immunization. The European Region faces challenges regarding political commitment to support immunization and respond to vaccine hesitancy and refusal. In the Western Pacific Region there is progress towards the goal of reducing chronic hepatitis B infections among 5 year-old children to <1% by 2017, although the implementation of the hepatitis B birth dose remains problematic. The South-East Asian Region is focusing on maternal and neonatal tetanus (MNT) elimination, for which challenges remain. In the Eastern Mediterranean Region the ongoing security situation in several countries has led to a decrease in routine vaccination coverage and an increase in measles cases in some areas. Nevertheless strong demand for immunization has avoided major decreases in vaccination coverage. Because infants are commonly contracting measles before 9 months of age in this Region, administration of a measles vaccine dose at 6 months of age is being considered; this issue is being reviewed by the SAGE Measles and Rubella Working Group.

A consultation on typhoid conjugate vaccines concluded that more data need to be generated for a SAGE review of policy recommendations. It is planned to establish a SAGE working group in 2016 to prepare for a SAGE review of the evidence in 2017. The RTS,S malaria vaccine final phase 3 data were reviewed by the Joint Technical Expert Group in September 2014 and a joint review session of SAGE and the Malaria Programme Advisory Committee will likely take place in October 2015. With the expected submission of dengue vaccine trial results to regulatory authorities in early 2015, a SAGE dengue working group will soon be convened.

Update on the Ebola epidemic

SAGE was provided with an overview of the current epidemic of Ebola virus disease in West Africa, which was declared a public health emergency of international concern under the International Health Regulations in August 2014. A United Nations Mission for Ebola Emergency Response (UNMEER) based in Accra, Ghana, has been established and a roadmap for responding to the outbreak has been developed.

A WHO Task Force is working to accelerate access to new therapeutic medicines and preventive vaccines to combat the Ebola epidemic. On 11 August 2014, a panel of ethicists reviewed ethical considerations[3] for use of unregistered interventions for Ebola. The consensus outcome of the meeting was that in the current context it is ethical to offer interventions with unknown efficacy and unknown adverse effects as potential treatment or prevention. However, the experts concluded that ethical, scientific and pragmatic criteria must guide

touchés où l'on a observé une baisse spectaculaire de la couverture vaccinale cette année. Le SAGE a relevé avec inquiétude que la flambée d'Ebola met en évidence la vulnérabilité de la Région africaine et que des mesures doivent être prises pour s'assurer que de futures crises ne remettent pas en cause les progrès de la vaccination. La Région des Amériques a récemment adopté une résolution pour garantir la couverture de santé universelle, vaccination comprise. La Région européenne se heurte à des difficultés concernant l'engagement politique pour soutenir la vaccination et réagir au phénomène d'hésitation à l'égard des vaccins ou de refus de ceux-ci. Dans la Région du Pacifique occidental, on note que des progrès ont été accomplis dans le but de ramener le taux des infections chroniques par le virus de l'hépatite B chez les enfants de 5 ans à <1% d'ici 2017, bien que l'administration d'une dose vaccinale à la naissance reste problématique. La Région de l'Asie du Sud-Est s'attache à éliminer le tétanos maternel et néonatal (TMN), domaine dans lequel des difficultés subsistent. Dans la Région de la Méditerranée orientale, les problèmes de sécurité actuels dans certains pays ont entraîné une baisse de la couverture de la vaccination systématique et une hausse du nombre des cas de rougeole dans certaines zones. Néanmoins, la forte demande pour la vaccination a permis d'éviter des diminutions importantes de la couverture. Comme les nourrissons contractent couramment la rougeole avant l'âge de 9 mois dans cette Région, on envisage l'administration d'une dose de vaccin antirougeoleux à l'âge de 6 mois; cette question est actuellement examinée par le Groupe de travail du SAGE sur la rougeole et la rubéole.

Une consultation sur les vaccins conjugués contre la typhoïde a conclu qu'il fallait obtenir davantage de données avant que le SAGE examine les recommandations politiques. Il est prévu de mettre en place un groupe de travail en 2016 en vue d'un examen des données factuelles par le SAGE en 2017. Les données finales de la phase 3 pour le vaccin antipaludique RTS,S ont été étudiées par le Groupe conjoint d'experts techniques en septembre 2014 et une session conjointe du SAGE et du Comité consultatif du Programme de lutte antipaludique se tiendra probablement en octobre 2015. Avec la soumission des résultats de l'essai de vaccin contre la dengue aux autorités réglementaires attendue début 2015, un groupe de travail du SAGE sur la dengue sera bientôt réuni.

Le point sur la flambée d'Ebola

Le SAGE a pris connaissance d'une présentation générale de l'épidémie actuelle de maladie à virus Ebola en Afrique de l'Ouest, déclarée en août 2014 urgence de santé publique de portée internationale au titre du Règlement sanitaire international. La Mission des Nations Unies pour l'action d'urgence contre l'Ebola (MINUAUCE), basée à Accra (Ghana), a été mise en place et une feuille de route a été élaborée pour riposter à la flambée.

Un groupe spécial de l'OMS s'efforce d'accélérer l'accès à de nouveaux médicaments thérapeutiques et vaccins préventifs pour combattre l'épidémie. Le 11 août 2014, un tableau d'experts a examiné les considérations éthiques[3] liées à l'utilisation d'interventions non homologuées contre la maladie à virus Ebola. Les participants ont conclu à l'unanimité que, dans la situation actuelle, il est conforme à l'éthique de proposer, comme moyens potentiels de prévention ou de traitement, des interventions dont on ne connaît pas l'efficacité et les effets secondaires. En revanche, ils ont également indiqué que la prestation de telles

[3] Ethical considerations for use of unregistered interventions for Ebola virus disease. Report of an advisory panel to WHO http://www.who.int/csr/resources/publications/ebola/ethical-considerations/en/

[3] Considérations éthiques liées à l'utilisation d'interventions non homologuées contre la maladie à virus Ebola. Rapport à l'OMS d'un groupe consultatif. http://www.who.int/csr/resources/publications/ebola/ethical-considerations/fr/.

the provision of such interventions. In addition, there is a moral duty to evaluate these interventions using the best possible research designs to establish their safety and efficacy. A consultation on potential Ebola vaccines and therapies followed (4–5 September 2014[4]) to review plans for safety studies of 2 candidate vaccines – one utilizing a vesicular stomatitis virus (rVSV-ZEBOV) and another utilizing a chimpanzee adenovirus (ChAD3-ZEBOV), both expressing Ebola Zaire surface glycoproteins. Randomized controlled trials (RCTs) are the best study design, but when not feasible, alternatives may be considered, including cluster-randomized and step-wedge designs. The consultation noted that investigation of any candidate intervention must not detract attention from implementation of effective clinical care, rigorous infection prevention and control, careful contact tracing and follow-up, effective risk communication, and social mobilization.

On 29–30 September 2014,[5] WHO convened a consultation on study designs for Ebola vaccines which reiterated the preference for well-designed RCTs, and if not feasible, alternative designs such as a step-wedge approach.

SAGE was updated on the current status of clinical development of the 2 leading candidate vaccines. Ten phase 1 studies of the safety of the vaccines are planned or initiated, to start in the USA or Europe and then move rapidly to Africa. Initial data from these trials, involving approximately 250 subjects for each vaccine, would be available in late November-early December. Provided that the data support further study, the near-term development plans foresee pre-exposure study in both non-affected and affected countries, starting early in 2015. It was acknowledged that the current planning process was very dynamic with extraordinary efforts made to accelerate scale-up of vaccine production and plans for use in countries. New partners were engaging in the response and SAGE took note that the Gavi Board had requested to be presented with options for speeding up the availability of a potential Ebola vaccine at its December 2014 meeting. The presentation by Gavi (below) mentioned a third vaccine candidate – Ad26/MVA-BN expressing Ebola virus genes – which is not yet in phase 1 trials.

SAGE confirmed that it would provide expert advice on the deployment of Ebola vaccines on an emergency basis, as needed in response to requests from WHO. Subsequently SAGE was asked to immediately establish a SAGE working group on Ebola vaccines and vaccination.[6]

SAGE also endorsed calls for capacity building for preparedness to respond to future infectious disease threats, including supporting requests to transfer lessons learnt from the accelerated regulatory review process for candidate Ebola vaccines to other potential vaccines of major public health importance.

interventions devait satisfaire à des critères éthiques, scientifiques et pragmatiques. De plus, il y a une obligation morale de les évaluer en utilisant les meilleurs schémas possibles d'étude pour en établir l'efficacité et l'innocuité. Une consultation sur les traitements et vaccins potentiels contre le virus Ebola s'en est suivie (4-5 septembre 2014)[4] pour étudier les plans concernant les études d'innocuité de 2 vaccins candidats – l'un utilisant le virus de la stomatite vésiculaire (rVSV-ZEBOV) et l'autre un adénovirus de chimpanzé (ChAD3-ZEBOV), exprimant dans les 2 cas les glycoprotéines de surface du virus Ebola Zaïre. Si les essais contrôlés randomisés représentent le meilleur schéma, lorsqu'ils ne sont pas faisables, d'autres alternatives ou schémas peuvent être envisagés, notamment des essais randomisés en cluster ou des essais de type «step-wedge» (application séquentielle de l'intervention). La consultation a noté que les études sur des interventions candidates ne doivent pas détourner l'attention de la mise en œuvre de soins cliniques efficaces, d'une lutte rigoureuse contre l'infection, de la recherche et du suivi minutieux des contacts, d'une communication efficace sur le risque et de la mobilisation sociale.

Les 29 et 30 septembre 2014,[5] l'OMS a organisé une consultation sur les schémas d'études pour les vaccins contre Ebola, qui a exprimé de nouveau la préférence pour des essais contrôlés randomisés bien conçus et, s'ils ne sont pas faisables, des schémas de remplacement comme l'approche de type «step-wedge».

Le SAGE a été informé du stade actuel du développement clinique des 2 principaux vaccins candidats. Dix études de phase 1 sur leur innocuité sont planifiées ou ont commencé, d'abord aux États-Unis ou en Europe puis rapidement en Afrique. Les données initiales de ces essais, portant sur environ 250 sujets pour chaque vaccin, seront disponibles fin novembre ou début décembre. Dans la mesure où les données étayent la poursuite des études, les plans de développement à court terme prévoient une étude préexposition à la fois dans les pays exempts et les pays affectés, qui commencera au début de l'année 2015. Les membres ont reconnu que le processus actuel de planification est très dynamique, avec des efforts extraordinaires pour accélérer l'extension de la production des vaccins et les plans pour leur utilisation dans les pays. De nouveaux partenaires s'engagent dans la riposte et le SAGE a pris note de la requête du Conseil de Gavi, l'Alliance du Vaccin (Gavi) demandant qu'on lui présente des options pour accélérer la mise à disposition d'un vaccin potentiel contre Ebola lors de sa réunion en décembre 2014. La présentation faite par Gavi (ci-après) a mentionné un troisième vaccin candidat, Ad26/MVA-BN, qui exprime des gènes du virus Ebola mais n'a pas encore atteint les essais cliniques de phase 1.

Le SAGE a confirmé qu'il donnerait l'avis des experts sur le déploiement en urgence des vaccins contre Ebola, selon les besoins et en fonction des demandes de l'OMS. Par conséquent, il a été demandé au SAGE de créer immédiatement un groupe de travail sur les vaccins et la vaccination contre le virus Ebola.[6]

Le SAGE a également approuvé les appels à un renforcement des capacités pour se préparer à riposter à de futures menaces de maladies infectieuses. Il soutient notamment les demandes relatives au transfert des enseignements tirés du processus accéléré d'examen réglementaire pour les vaccins candidats contre Ebola à d'autres vaccins potentiels pouvant avoir une importance majeure pour la santé publique.

[4] Consultation on potential Ebola therapies and vaccines http://www.who.int/mediacentre/events/meetings/2014/ebola-interventions/en/

[5] WHO consultation on Ebola available at http://www.who.int/immunization/diseases/ebola/WHO_consultation_ebola_sep2014/en/

[6] See http://www.who.int/immunization/policy/sage/sage_wg_ebola_nov14/en/

[4] Consultation sur les traitements et vaccins potentiels contre le virus Ebola http://www.who.int/mediacentre/events/meetings/2014/ebola-interventions/fr/

[5] Consultation de l'OMS sur Ebola disponible à l'adresse suivante: http://www.who.int/immunization/diseases/ebola/WHO_consultation_ebola_sep2014/en/

[6] Voir http://www.who.int/immunization/policy/sage/sage_wg_ebola_nov14/en/

Report from Gavi, the Vaccine Alliance

The Managing Director of Policy and Performance updated SAGE on the Gavi Board approved strategic framework for 2016–2020, current policies under review, progress towards achieving the 2015 goals and Gavi's replenishment meeting in January 2015 aimed at raising US$ 7.5 billion over the next 5 years.

In June 2014, the Board approved the new strategic framework, which remains focused on saving children's lives and protecting people's health by increasing equitable use of vaccines in lower income countries. The framework includes 4 strategic goals, with a renewed focus on country leadership, management and coordination, monitoring and evaluation.

The next steps in finalizing the new strategic process include setting global level indicators and establishing mechanisms for tracking progress, including finalizing indicators of the Fully Immunized Child, coverage by antigen and equity of coverage indicators.

In terms of policy updates, the eligibility, co-financing and graduation policies are under review, towards ensuring successful graduation and sustainability of Gavi support in the 22 countries projected to graduate by 2020. Co-financing remains an important issue for Gavi's replenishment with countries' cumulative value of co-financing expected to total US$ 1.2 billion by 2020. Concerns remain regarding the ability of countries to graduate given the increasing number of vaccines to be deployed, driving the cost to over US$ 100 per fully immunized child. Its Programme and Policy Committee requested Gavi to develop options beyond Gavi-eligible countries for a pooled procurement facility.

The Board has requested the Gavi secretariat to explore the potential role of Gavi in financing Ebola vaccines, for discussion by the Board in December 2014.

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

At its June 2014 meeting,[7] for its 15th anniversary, GACVS reviewed its accomplishments and new challenges in view of the evolving public health environment. Discussions highlighted the needs for particular consideration of: (i) the evolving technical aspects of vaccine pharmacovigilance; (ii) process issues related to GACVS operations; and (iii) communication of GACVS findings.

GACVS also discussed the: (i) safety of a novel live attenuated rotavirus vaccine; (ii) safety of the licensed recombinant hepatitis E vaccine; (iii) the safety of meningococcal A conjugate vaccine during pregnancy; and (iv) preparation for malaria vaccine introduction.

Report from the Immunization Practices Advisory Committee (IPAC)

At its September 2014 meeting, IPAC addressed inter alia: (i) home-based vaccination records as important contributors to improving coverage and community en-

[7] See No 21, 2014, pp. 253–260.

Rapport de Gavi, l'Alliance du Vaccin

Le Directeur de gestion pour la Politique et les performances a informé le SAGE du cadre stratégique approuvé par le Conseil de l'Alliance pour 2016-2020, des politiques actuelles en cours d'examen, des progrès accomplis dans la réalisation des buts fixés pour 2015 et de la réunion pour la reconstitution des ressources de l'Alliance, qui aura lieu en janvier 2015 et vise à lever US$ 7,5 milliards pour les 5 prochaines années.

En juin 2014, le Conseil a approuvé le nouveau cadre stratégique, qui reste axé sur les vies d'enfants à sauver et sur la protection de la santé des populations en renforçant l'usage équitable des vaccins dans les pays à faible revenu. Le cadre comporte 4 buts stratégiques, mettant de nouveau l'accent sur le leadership des pays, la gestion et la coordination, le suivi et l'évaluation.

Les prochaines étapes pour finaliser le nouveau processus stratégique comprennent la détermination d'indicateurs au niveau mondial et la mise en place de mécanismes pour suivre les progrès, avec la finalisation des indicateurs pour l'enfant totalement vacciné, la couverture par antigène et l'équité de la couverture.

En termes d'actualisation des politiques, celles concernant l'éligibilité, le cofinancement et la qualification sont en cours d'examen, dans le but d'assurer le succès des qualifications et la pérennité de l'aide de Gavi dans les 22 pays qui, selon les projections, se qualifieront d'ici 2020. Le cofinancement reste un sujet important pour la reconstitution des ressources de l'Alliance, avec une valeur cumulée du cofinancement par les pays devant atteindre US$ 1,2 milliard d'ici 2020. Des inquiétudes demeurent quant à la capacité des pays à se qualifier au vu du nombre croissant de vaccins qu'ils ont à déployer, le coût d'un enfant totalement vacciné dépassant les US$ 100. Le Comité du programme et des politiques a demandé à l'Alliance d'élaborer des options dépassant le cadre des pays pouvant prétendre à l'aide de Gavi pour instituer un système d'achats groupés.

Le Conseil a demandé au secrétariat de Gavi d'étudier son rôle potentiel dans le financement des vaccins contre Ebola, sujet dont il discutera en décembre 2014.

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

Lors de sa réunion en juin 2014,[7] à l'occasion de son quinzième anniversaire, le Comité a passé en revue ses accomplissements et les nouveaux défis dans le contexte évolutif de l'environnement de la santé publique. Il ressort des discussions le besoin de prendre particulièrement en compte: i) l'évolution des aspects techniques de la pharmacovigilance dans le domaine des vaccins; ii) les problèmes de méthode liés aux opérations du Comité; et iii) la communication des conclusions du Comité.

Le Comité a également discuté de: i) l'innocuité d'un nouveau vaccin antirotavirus vivant atténué; ii) l'innocuité du vaccin anti-hépatite E recombinant homologué; iii) l'innocuité du vaccin conjugué contre le méningocoque A pendant la grossesse; et iv) la préparation à l'introduction du vaccin antipaludique.

Rapport du Comité consultatif sur les pratiques vaccinales (IPAC)

Lors de sa réunion en septembre 2014, le Comité s'est intéressé entre autres: i) aux carnets de vaccination conservés à domicile comme des éléments importants contribuant à l'amélioration de

[7] Voir N° 21, 2014, pp. 253-260.

gagement; (ii) revisions to the WHO procedures for assessing Programmatic Suitability of Vaccine Candidates for WHO prequalification; (iii) field study outcomes in Viet Nam and Senegal on the use of a compact pre-filled auto-disable device for vaccination; and (iv) immunization supply chain and logistics. IPAC also reported on its new operating modality, intended to strengthen timely expert advice on programmatic issues for existing or new WHO advisory work streams. SAGE welcomed this shifted focus aimed at facilitating a comprehensive programmatic perspective in the development of policy recommendations. SAGE requested future update on approaches to prioritization within supply chain improvement plans.

Report from the Immunization and Vaccine related Implementation Research Advisory Committee (IVIR-AC)

At its September 2014 meeting, IVIR-AC addressed 15 topics, 3 of which were highlighted for SAGE: (i) missed opportunities for immunization; (ii) WHO's vaccine preventable disease burden and impact assessment framework; and (iii) the revised method for WHO coverage surveys. The inclusion of qualitative research in the scope of IVIR-AC was discussed and it was felt that the current terms of reference should reflect IVIR-AC's role in behavioural qualitative research. The potential to involve WHO collaborating centres in developing evidence, tools, and methodologies was discussed, particularly for the African Region. SAGE also noted that a sub-group of IVIR-AC members and external subject experts will make recommendations on the types of prospective studies to assess the non-specific effects of vaccines, and that links between the WHO Alliance for Health Policy and Health Systems Research and IVIR-AC could be useful in priority setting and discussions.

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

PDVAC met for the first time in September 2014. This committee was established to advise the Initiative for Vaccine Research (IVR – a team of the IVB Department) on its workplan on an annual basis. If IVR decides to initiate activities in a given area for upstream vaccine research and developments (R&D) (defined as pre-clinical to the phase 2 stage of clinical evaluation), these activities will include guidance on trial design for data generation to support global use (focusing on low-income countries' needs), development of Preferred Product Characteristics to inform Target Product Profiles used by vaccine developers, and in some cases vaccine R&D roadmaps on a pathogen-specific basis. WHO will not engage directly in product development, and will focus on the above areas to reduce timelines for vaccine availability in order to address unmet global public health needs by providing guidance to funding agencies and vaccine developers.

PDVAC highlighted 3 priority pathogens for which there is a clear unmet public health need, reasonable proba-

la couverture et à l'engagement de la communauté; ii) aux révisions des procédures de l'OMS pour évaluer l'adéquation des vaccins candidats au regard des programmes en vue de leur préqualification par l'Organisation; iii) aux résultats d'une étude sur le terrain au Viet Nam et au Sénégal sur l'utilisation d'un dispositif compact pré-rempli et autobloquant pour la vaccination; et iv) à la chaîne d'approvisionnement et à la logistique pour la vaccination. Le Comité a également présenté ses nouvelles modalités de fonctionnement, visant à ce que les experts rendent leur avis plus rapidement sur les questions programmatiques liées aux activités de conseil de l'OMS, existantes ou nouvelles. Le SAGE s'est félicité de ce changement visant à faciliter une perspective programmatique étendue dans l'élaboration des recommandations politiques. Il a demandé qu'on l'informe à l'avenir des approches adoptées pour l'établissement des priorités dans le cadre des plans d'amélioration de la chaîne d'approvisionnement.

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

Lors de sa réunion en septembre 2014, le Comité a étudié 15 sujets, dont 3 ont été mis en exergue à l'intention du SAGE: i) les occasions manquées pour la vaccination; ii) le cadre OMS d'évaluation de la charge des maladies à prévention vaccinale et de leur impact; et iii) la méthode révisée pour les enquêtes de couverture de l'OMS. L'intégration de la recherche qualitative dans le champ d'action du Comité a fait l'objet d'une discussion et on a estimé que l'on devait retrouver dans le mandat actuel le rôle du Comité en matière de recherche qualitative sur les comportements. La possibilité d'impliquer des centres collaborateurs de l'OMS pour obtenir des données factuelles et mettre au point des outils et des méthodes a été abordée, en particulier pour la Région africaine. Le SAGE a également pris note qu'un sous-groupe réunissant des membres du Comité et des experts externes sur le sujet fera des recommandations sur les types d'études prospectives pour évaluer les effets non spécifiques des vaccins et que les liens entre l'Alliance de l'OMS pour la recherche sur les politiques et les systèmes de santé avec le Comité IVIR-AC pourraient être utiles pour la définition des priorités et les discussions.

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

Le Comité s'est réuni pour la première fois en septembre 2014. Il a été créé pour donner une fois par an des conseils à l'Initiative pour la recherche sur les vaccins (IVR, une équipe du Département IVB) sur son plan de travail. Si l'IVR décide d'entreprendre des activités dans un domaine donné pour orienter en amont la recherche-développement de vaccins (R&D) (définie comme l'évaluation préclinique et clinique jusqu'à la phase 2 des essais), celles-ci comporteront des orientations sur les schémas des essais pour produire des données étayant un usage mondial (en s'orientant sur les besoins des pays à faible revenu), la mise au point des caractéristiques préférées des produits pour orienter les profils de produits cibles utilisés par ceux qui mettent au point les vaccins et, dans certains cas, des feuilles de route pour la recherche-développement de vaccins sur une base spécifique aux agents pathogènes. L'OMS ne s'engagera pas directement dans la mise au point de produits et se concentrera sur les domaines susnommés pour raccourcir les délais de disponibilité des vaccins afin de répondre aux besoins non satisfaits de la santé publique mondiale, en donnant des orientations aux bailleurs de fonds et à ceux qui mettent les vaccins au point.

Le Comité a mis en exergue 3 agents pathogènes prioritaires selon 3 critères: il apparaît clairement que les besoins de la

bility of new vaccine product(s) emerging from the pipeline by 2020, and a potential substantial role for WHO in advancing timelines for licensure of high quality, safe and effective vaccines. These are Respiratory Syncytial Virus, Group B Streptococcal and Group A Streptococcal vaccines.

Upstream enteric vaccine development was highlighted as a gap in IVR's activities, and should be initiated if resources can be mobilized. Enterotoxigenic *Escherichia coli*, Shigella and Norovirus were noted by PDVAC as pathogens for which provision of guidance would be warranted.

Development of Preferred Product Characteristics for improved multi-seasonal influenza vaccines was discussed as another area where guidance may be valuable.

A group of neglected parasitic diseases with substantial disease burden were considered including human hookworm, leishmaniasis, schistosomiasis and Chagas disease. PDVAC asked that the product development community in these areas prepare a document with the clinical development and licensure pathways and criteria for progression.

IVR activities will continue in HIV, tuberculosis, malaria and universal influenza vaccines. Malaria work includes a focus on the regulatory pathway for transmission-blocking vaccines and a continued focus on highly efficacious second generation vaccines to prevent morbidity and mortality.

PDVAC will assess a differing range of novel pathogens each year, with suggestions for next year including *Staphylococcus aureus*, chikungunya, dengue, and potentially filovirus and other emerging viral pathogens.

SAGE requested to be updated by PDVAC on the criteria used for prioritizing vaccines for IVR's work.

Report from the Expert Committee on Biological Standardization (ECBS)

At its October 2014 meeting ECBS adopted 3 written standards: (i) recommendations to assure quality, safety, and efficacy of inactivated polio vaccine (IPV); (ii) guidelines on procedures and data requirements for changes to approved vaccines; and (iii) guidance on scientific principles for regulatory risk evaluation on finding an adventitious agent in a marketed vaccine. Physical standards created in 2014 included the first international reference reagent of anti-malaria human serum. Recognizing that regulatory preparedness is critical for rapid access to licensed vaccines, ECBS has established a subgroup to assist WHO on Ebola vaccine regulatory issues.

Global Vaccine Action Plan: assessment of progress

The independent assessment of progress against the GVAP goals[8] and strategic indicators followed the pro-

santé publique ne sont pas couverts, il y a une probabilité raisonnable que de nouveaux produits vaccinaux émergent des filières de développement d'ici 2020 et l'OMS a un rôle substantiel à jouer pour raccourcir les délais d'homologation de vaccins de qualité sûrs, et efficaces. Il s'agit du virus respiratoire syncytial, des streptocoques B et des streptocoques A.

Il ressort clairement des activités d'IVR qu'une des lacunes a trait au développement en amont d'un vaccin entérique, que l'on devrait entreprendre si on peut mobiliser des ressources. Le Comité a relevé qu'*Escherichia coli* entérotoxinogène, Shigella et Norovirus sont des agents pathogènes pour lesquels des orientations seraient justifiées.

Le Comité a également parlé de l'élaboration des caractéristiques préférées des produits pour des vaccins antigrippaux actifs plusieurs saisons comme d'un autre domaine dans lequel des orientations serait utiles.

Un groupe de maladies parasitaires négligées associées à une forte charge de morbidité, dont l'ankylostomiase humaine, la leishmaniose, la schistosomiase et la maladie de Chagas, a également été étudié. Le Comité a demandé aux milieux s'occupant du développement des produits dans ce domaine de préparer un document indiquant les voies pour la mise au point clinique et l'homologation, ainsi que les critères de progression.

L'Initiative poursuivra ses activités dans le domaine des vaccins contre le VIH, la tuberculose, le paludisme et le vaccin universel contre la grippe. Pour le paludisme, les travaux devront mettre l'accent sur les voies réglementaires pour les vaccins bloquant la transmission et continuer de s'intéresser aux vaccins hautement efficaces de seconde génération pour éviter la morbidité et la mortalité.

Le Comité évaluera chaque année un groupe différent de nouveaux agents pathogènes, avec des propositions pour l'année suivante concernant *Staphylococcus aureus*, le chikungunya, la dengue, des filovirus potentiels et d'autres virus pathogènes émergents.

Le SAGE a demandé au Comité de l'informer des critères utilisés dans l'établissement des vaccins prioritaires pour les travaux de l'Initiative.

Rapport du Comité d'experts de la standardisation biologique (ECBS)

Lors de sa réunion en octobre 2014, le Comité a adopté 3 normes écrites: i) recommandations pour assurer la qualité, l'innocuité et l'efficacité du vaccin antipoliomyélitique inactivé (VPI); ii) lignes directrices sur les procédures et les données exigées pour les modifications apportées aux vaccins homologués; et iii) orientations sur les principes scientifiques de l'évaluation règlementaire du risque de trouver un agent contaminant dans un vaccin commercialisé. Des étalons physiques ont été créés en 2014, dont le premier réactif de référence internationale du sérum humain antipaludique. Reconnaissant que la préparation réglementaire est essentielle pour un accès rapide aux vaccins homologués, le Comité a constitué un sous-groupe devant assister l'OMS sur les questions réglementaires liées aux vaccins contre Ebola.

Plan d'action mondial pour les vaccins: évaluation des progrès

L'évaluation indépendante des progrès par rapport aux buts du GVAP[8] et des indicateurs stratégiques a suivi le processus exposé

[8] See http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/

[8] Voir http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/

cess laid out in the Monitoring, Evaluation and Accountability Framework. As in 2013, the GVAP secretariat prepared a detailed report[9] on progress against each of the GVAP indicators. The report also reflected progress with research and development indicators, which is reported only biennially. Progress against 2 new indicators, one of vaccine stock-out and another on integrated approaches, was included in the report. This was supplemented with additional inputs from the CSOs and vaccine manufacturers.

The secretariat report was reviewed by the SAGE Working Group for the Decade of Vaccines and served as the basis of its assessment report, which was presented to SAGE. The salient findings of the report and the main recommendations made by SAGE are briefly summarized below.

The GVAP set 6 key immunization targets with deadlines at the end of 2014 or 2015, of which 5 are not on track to be achieved (DTP3 coverage, interruption of poliovirus transmission, elimination of MNT, elimination of measles and elimination of rubella). Some targets with deadlines that pre-dated GVAP have been missed multiple times before. Although these targets relate to different diseases, common factors explain this delay: failure to extend vaccination services to people who cannot currently access them, and failure to strengthen the health-care system so that all doses of vaccine are reliably provided.

However, there has been success in introducing new vaccines, and achievements in numerous countries in several areas such as the establishment and strengthening of National Immunization Technical Advisory Groups. The GVAP was created to end the inequity in vaccination coverage worldwide, and thereby save millions of lives. This need remains as important and urgent as ever and failure to deliver at the required scale is not acceptable.

This report highlights 5 areas that require priority action:

- Implementation of the GVAP, which has remained patchy and slow 3 years after its start date.
- Poor quality and inadequate use of data, which is substantially impeding programme management and improvement.
- The affordability and supply of vaccines, which may be a significant problem for many countries. In addition the current lack of adequate information hinders understanding and corrective action.
- Basic failures of integration between immunization and other health programmes mean that health-care workers are repeatedly missing easy opportunities to offer vaccinations during clinic visits for other problems.
- Disruptive situations, including war and major disease outbreaks (such as Ebola, currently) have impeded vaccine delivery. Despite such situations, vaccines must be delivered.

SAGE concurred with the main conclusions from the Working Group and recommended that:

dans le cadre de suivi, d'évaluation et de responsabilisation. Comme en 2013, le secrétariat du GVAP a préparé un rapport détaillé[9] sur les progrès accomplis en fonction de chacun des indicateurs du Plan. On retrouve aussi dans ce document les progrès pour les indicateurs de la recherche-développement, dont il n'est rendu compte que tous les 2 ans. Les progrès par rapport à 2 nouveaux indicateurs, l'un sur les ruptures de stock de vaccin et l'autre sur les approches intégrées, ont également été inclus. Le tout a été complété par des contributions supplémentaires émanant des organisations de la société civile et des fabricants de vaccins.

Le rapport du secrétariat a été examiné par le groupe de travail du SAGE sur la Décennie de la vaccination et a servi de base pour son rapport d'évaluation, présenté au SAGE. Les observations les plus saillantes et les principales recommandations faites par le SAGE sont brièvement récapitulées ci-après.

Le GVAP fixe pour la vaccination 6 cibles essentielles avec des dates butoirs fin 2014 ou fin 2015, dont 5 ne sont pas en voie d'être atteintes (couverture du DTC3, interruption de la transmission du poliovirus, élimination du TMN, élimination de la rougeole et élimination de la rubéole). Certaines cibles avec des dates butoirs fixées avant le GVAP ont été manquées à de multiples reprises. Bien que chacune d'elles ait trait à une maladie différente, le retard s'explique par des facteurs communs: échec de l'extension des services de vaccination dans des populations qui n'y ont pour l'instant pas accès et échec du renforcement des systèmes de santé de façon à pouvoir assurer un approvisionnement fiable en vaccins.

L'introduction de nouveaux vaccins a connu cependant un certain succès et il y a eu des changements positifs dans de nombreux pays et dans plusieurs domaines, comme la création et le renforcement des groupes consultatifs techniques nationaux sur la vaccination. Le GVAP a été créé pour mettre fin aux inégalités de la couverture vaccinale dans le monde et ainsi sauver des millions de vies. Ce besoin demeure toujours aussi important et urgent et il n'est pas acceptable de ne pas arriver à dispenser ce service à l'échelle nécessaire.

Le rapport met en exergue 5 domaines d'action prioritaires:

- Trois ans après son lancement, la mise en œuvre du GVAP demeure parcellaire et lente.
- La mauvaise qualité et l'utilisation insuffisante des données constituent une entrave importante à la gestion et à l'amélioration du programme.
- L'accessibilité financière des vaccins et l'approvisionnement peuvent poser un problème important dans beaucoup de pays. De plus, le manque actuel d'informations adéquates empêche de saisir la situation et de prendre des mesures correctives.
- Les défauts basiques d'intégration entre la vaccination et d'autres programmes de santé aboutissent à ce que les agents de santé manquent de manière répétée des occasions faciles de proposer les vaccinations lors des consultations pour d'autres problèmes.
- La distribution des vaccins s'est heurtée à des situations de déstabilisation, comme des guerres ou des flambées épidémiques majeures (telles qu'Ebola actuellement). Malgré ces situations, il faut tout de même assurer la distribution des vaccins.

Le SAGE souscrit aux principales conclusions du groupe de travail et a recommandé que:

[9] See http://www.who.int/immunization/global_vaccine_action_plan/en/

[9] Voir http://www.who.int/immunization/global_vaccine_action_plan/en/

- The Director-General of WHO, during the 68th World Health Assembly in 2015, convene side meetings in collaboration with the GVAP secretariat agencies. For countries with routine vaccination (DTP3) coverage of <80%, to which each Minister of Health will be asked to report on their challenges, plans and timelines to improve coverage to meet the GVAP goals.
- The SAGE's GVAP assessment reports remain as standing items at the WHA until 2020.

- Failure to achieve the 2013 milestone for MNT elimination is largely related to the funding gap. Partners should lead a concerted effort to fill this gap, by refreshing the communication approach and seeking novel partners for this vital, and repeatedly missed, goal.
- Regions and countries rapidly finalize their own vaccine action plans based on the GVAP, using this assessment report as a further guide and establishing bodies to guide and monitor implementation.

- Countries give CSOs substantially more formal involvement in the delivery and improvement of vaccination services, establishing clear responsibilities for which they are accountable.

- After consulting with their respective Regional Technical Advisory Group, every Region establish a regional verification commission, and after consulting with their respective National Immunization Technical Advisory Group, every country explore options for establishing a national verification commission, to scrutinize and monitor progress towards the measles elimination targets.
- The heads of the GVAP secretariat agencies (the Bill and Melinda Gates Foundation, Gavi, the US National Institute of Allergy and Infectious Diseases, WHO and UNICEF) meet to consider this report and agree on specific corrective actions.
- The heads of GVAP secretariat agencies report to the 2015 World Economic Forum on the plan's establishment, its lack of progress so far and what forum participants – who supported the Decade of Vaccines concept in 2010 – can do to help its implementation.

- Countries invest in improving data quality at the local level, and use data to strengthen accountability and to improve understanding of the programmatic issues.
- Technical agencies further develop and deploy tools to help countries with limited personnel with the practical task of improving the quality and use of data.

- Technical agencies conduct urgent assessments of (i) the extent to which the reported national-level stock-outs are affecting local vaccine supply and delivery, and (ii) the root causes of these stock-outs.
- Countries change their approach to vaccine affordability, creating transparency by making pricing information publicly available, and by collaborating with WHO and all technical agencies to develop solutions.

- Le Directeur général de l'OMS, au cours de la 68e Assemblée mondiale de la Santé en 2015, organise des réunions parallèles en collaboration avec les agences du secrétariat du GVAP pour les pays ayant une couverture de la vaccination systématique par DTC3 <80%, au cours desquelles il sera demandé à chaque ministre de la santé de faire un rapport sur les difficultés, les plans et les délais pour améliorer la couverture afin d'atteindre les objectifs du GVAP.
- Les rapports d'évaluation du SAGE sur le GVAP restent un point permanent à l'ordre du jour de l'Assemblée mondiale de la Santé jusqu'en 2020.
- Le fait de ne pas avoir atteint la cible de l'élimination du TMN en 2013 est dû en grande partie au déficit de financement. Les partenaires devraient mener un effort concerté pour combler ce déficit, renouveler les méthodes de communication et chercher de nouveaux partenaires pour ce but crucial, qui a été manqué à plusieurs reprises.
- Les Régions et les pays finalisent rapidement leurs propres plans d'action pour les vaccins en se basant sur le GVAP, en se servant du présent rapport d'évaluation comme d'un guide et en instituant des organismes pour orienter et suivre la mise en œuvre.
- Les pays confient aux organisations de la société civile un rôle officiel sensiblement plus important dans la prestation et l'amélioration des services de vaccination, en établissant clairement des responsabilités pour lesquelles elles devront rendre des comptes.
- Après consultation des groupes consultatifs techniques régionaux respectifs, chaque Région met en place une commission régionale de vérification et, après consultation des groupes consultatifs techniques nationaux respectifs sur la vaccination, chaque pays examine les options pour mettre en place une commission nationale de vérification chargée de contrôler de près et de suivre les progrès accomplis en vue des cibles d'élimination de la rougeole.
- Les chefs des agences du secrétariat du GVAP (Fondation Bill & Melinda Gates, Gavi, *National Institute of Allergy and Infectious Diseases* des États-Unis, OMS et UNICEF) se réunissent pour examiner le présent rapport et décident des mesures correctives spécifiques.
- Les chefs des agences du secrétariat du GVAP font rapport au Forum économique mondial à Davos en 2015 sur la mise en place du Plan, sur le manque de progression jusqu'à présent et sur ce que les participants au Forum, qui ont apporté leur soutien à l'idée de la Décennie de la vaccination en 2010, peuvent faire pour contribuer à sa mise en œuvre.
- Les pays investissent dans l'amélioration de la qualité des données au niveau local, leur utilisation pour renforcer la responsabilisation et mieux connaître la nature des problèmes au niveau des programmes.
- Les agences techniques continuent d'élaborer et de déployer des outils pour aider les pays qui ont un personnel limité, à améliorer, dans la pratique, la qualité et l'utilisation des données.
- Les agences techniques évaluent d'urgence: i) la mesure dans laquelle les ruptures de stock au niveau national affectent l'approvisionnement en vaccins et leur distribution au niveau local et ii) les causes profondes de ces ruptures de stock.
- Les pays changent leur approche pour l'accessibilité économique des vaccins et créent la transparence en publiant les informations sur les tarifs et en collaborant entre eux, ainsi qu'avec l'OMS et les agences techniques, pour élaborer des solutions.

- Technical partners support countries to improve the transparency of vaccine pricing. Technical agencies themselves should do everything possible to share pricing data.
- Countries conduct studies to understand how opportunities to vaccinate people are being missed by health-care workers and their systems, and act to reduce their incidence.
- WHO discuss and develop guidelines on how to fully integrate vaccination into the operation of all aspects of the health-care system and to reduce missed opportunities to vaccinate.
- Countries ensure that health-care workers understand and follow WHO or national guidelines on what does, and does not, contraindicate vaccination, particularly in relation to childhood febrile illness, so that vaccination is not avoided unnecessarily.
- Following adoption of the GVAP and subsequently revision and adoption of regional and national plans, countries have the responsibility to ensure that immunization goals are shared, discussed and fully adopted by health-care workers.
- WHO expand its existing guidance on immunization in humanitarian emergencies to detail how routine and other immunization services are best maintained despite disruptive situations such as war and disease outbreaks.

- Les partenaires techniques aident les pays à améliorer la transparence dans la tarification des vaccins. Les organismes techniques eux-mêmes doivent faire tout leur possible pour communiquer les informations sur les prix.
- Les pays font des études pour comprendre comment les agents de santé et les systèmes de santé passent à côté d'occasions de vacciner les patients et agissent pour réduire la fréquence du problème.
- L'OMS étudie et élabore des lignes directrices indiquant comment intégrer pleinement la vaccination dans tous les aspects du fonctionnement des systèmes de santé et comment réduire la fréquence des occasions manquées de vacciner.
- Les pays veillent à ce que les agents de santé comprennent et appliquent les lignes directrices de l'OMS ou les directives nationales sur ce qui constitue ou non une contre-indication pour la vaccination, en particulier en relation avec les maladies fébriles de l'enfance, de façon à ne pas éviter inutilement l'administration des vaccins.
- Suite à l'adoption du GVAP, puis à la révision ultérieure et à l'adoption des plans régionaux et nationaux, les pays ont la responsabilité de veiller à ce que les buts de la vaccination soient communiqués à leurs agents de santé, discutés avec eux et qu'ils les adoptent sans réserve.
- L'OMS étend ses orientations sur la vaccination dans les situations d'urgence humanitaire pour décrire en détail comment maintenir au mieux les services de vaccination systématique et autres malgré certaines situations de déstabilisation, comme les guerres ou les flambées épidémiques.

Japanese encephalitis vaccines

Japanese encephalitis (JE) is the leading cause of viral encephalitis in Asia. While most individuals living in endemic settings become infected during their life, clinically apparent cases of JE occur only in about 1 in 250 infections. For those who develop disease, 30% of cases are fatal and 30%–50% of survivors have permanent neurologic or psychiatric sequelae. There is no specific treatment for JE.

The first WHO prequalification of a JE vaccine occurred in July 2013 and currently there are 3 WHO prequalified JE vaccines. Gavi has opened a financing window to support mass vaccination campaigns against JE.

There are 4 different classes of JE vaccines: inactivated mouse brain-derived, inactivated cell based, live attenuated, and live chimeric JE vaccines. Because the mouse brain-derived vaccine profile is less desirable than those of new generation JE vaccines, including higher reactogenicity, variability of manufacturing quality, cost, number of doses required and need for repeat booster doses, mouse brain-derived vaccines should be replaced by the newer generation vaccines.

SAGE reviewed immunogenicity (there is an established correlate of protection) and effectiveness data for JE vaccines with the exception of the mouse brain-derived vaccines. All products reviewed demonstrated high and comparable levels of seroprotection shortly following vaccination. Although data following JE vaccinees over time is more limited, immunogenicity data from clinical studies that vaccinees followed 3 and 5 years after vaccination in endemic settings demonstrated acceptable levels of seroprotection. SAGE concluded there is currently insufficient evidence to make any recommendation regarding booster doses, contrary to some manu-

Vaccins contre l'encéphalite japonaise

L'encéphalite japonaise (EJ) est la principale cause d'encéphalite virale en Asie. Alors que la plupart des personnes vivant en zone d'endémie sont infectées au cours de leur vie, l'EJ clinique apparente ne survient que dans la proportion d'une infection sur 250 environ. Lorsque la maladie se développe, elle est mortelle dans 30% des cas et 30 à 50% de ceux qui survivent gardent des séquelles neurologiques ou psychiatriques définitives. Il n'existe pas de traitement spécifique.

La première préqualification d'un vaccin contre l'EJ par l'OMS date de juillet 2013 et il y a actuellement 3 vaccins préqualifiés contre cette maladie. Gavi a ouvert un «guichet» de financement pour soutenir les campagnes de vaccination de masse contre l'EJ.

Il existe 4 types de vaccins contre l'EJ: vaccin inactivé préparé sur tissu cérébral de souris, vaccin inactivé préparé sur culture de cellules, vaccin vivant atténué et vaccin chimère vivant. Comme les vaccins préparés à partir de tissu cérébral de souris ont un profil moins souhaitable que les vaccins anti-EJ de nouvelle génération, notamment une réactogénicité plus élevée, une variabilité de la qualité de fabrication, le coût, le nombre de doses requises et la nécessité de répéter les rappels, ils devraient être remplacés par des produits de nouvelle génération.

Le SAGE a examiné les données sur l'immunogénicité (il y a une corrélation établie de protection) et l'efficacité des vaccins contre l'EJ, à l'exception de ceux préparés sur tissu cérébral de souris. Pour tous les produits examinés, on a mis en évidence des niveaux élevés et comparables de séroprotection peu après la vaccination. Bien qu'on ait moins de données sur le suivi dans le temps des sujets vaccinés contre l'EJ, les renseignements sur l'immunogénicité obtenus à partir d'études cliniques montrent que les sujets vaccinés suivis pendant 3 et 5 ans après la vaccination dans des zones d'endémie ont révélé des niveaux acceptables de séroprotection. Le SAGE a conclu qu'il n'y avait pas pour l'instant de données probantes suffisantes pour recommander les doses de rappel,

facturers' recommendations. For non-endemic settings, data are limited, but suggest a more rapid waning of immunity for some vaccinees. Evidence in children is currently insufficient to indicate whether or when booster doses might be needed. Longer-term seroprotection data should be generated and countries are strongly encouraged to conduct rigorous vaccine failure monitoring to assess whether there may be a need for booster doses.

Vaccine effectiveness data for the live attenuated vaccine demonstrated a strong impact on JE. Assessments of the public health and economic impact of vaccination programmes show significant reductions in JE cases and economic burden of JE. When high coverage is achieved, JE disease in humans can be virtually eliminated while the virus remains in the environment.

Based on clinical evaluation, all inactivated Vero cell, live attenuated and live chimeric JE vaccines have demonstrated an acceptable safety profile. Some of the newer vaccine products have limited follow-up in post-licensure studies, which are important for detecting rare adverse events. The limited data available on co-administration with measles and measles-mumps-rubella vaccines show no interference regarding safety and immunogenicity and support co-administration in routine and campaign settings, but further studies are desirable, especially with other measles-containing and varicella vaccines.

SAGE concluded that JE vaccination should be extended to all areas where JE is recognized as a public health priority. Even if the number of JE-confirmed cases is low, because of challenges in surveillance and documenting cases, vaccination should be considered where there is an environment suitable for JE transmission (i.e. presence of animal reservoirs, ecological conditions supportive of virus transmission, and proximity to other countries or regions with known transmission) and plausibility that the disease burden is significant. Because JE is transmitted by mosquitoes and maintained in an enzootic cycle, vaccination protects only the vaccinated individual and does not lead to herd immunity; high vaccination coverage is therefore necessary. The available evidence demonstrates a limited impact of non-vaccine strategies, such as vector control, and such interventions should not divert efforts from JE vaccination.

SAGE reiterated that collecting vaccine failure data is a high priority in order to inform the possible need for future booster doses, which may vary by vaccine and transmission setting. Surveillance strengthening is needed to assess the burden of JE, inform vaccination strategies, identify breakthrough cases, monitor vaccine safety for possible rare adverse events, and monitor the impact and effectiveness of JE vaccines. There is a need to develop standardized neutralization assay reagents and to ensure the availability of sensitive, specific, affordable commercial serological assays for testing in endemic countries.

contrairement à ce que préconisent certains fabricants. Dans les régions où la maladie n'est pas endémique, les données sont limitées mais laissent à penser que l'immunité décline plus rapidement chez certains sujets vaccinés. On n'a pas pour l'instant assez de données factuelles chez l'enfant pour indiquer si et quand des doses de rappel sont nécessaires. Des données sur la séroprotection à plus long terme devront être obtenues et l'on encourage fortement les pays à contrôler rigoureusement les échecs vaccinaux pour évaluer la nécessité éventuelle de doses de rappel.

Les données sur l'efficacité du vaccin vivant atténué ont mis en évidence un effet important sur l'EJ. Les évaluations portant sur l'impact des programmes de vaccination en santé publique et au niveau économique révèlent une baisse sensible du nombre des cas d'EJ et du poids économique de cette maladie. En parvenant à instaurer une couverture élevée, la maladie peut être pratiquement éliminée chez l'homme, alors que le virus subsiste dans l'environnement.

Sur la base des évaluations cliniques, il est démontré que le vaccin inactivé préparé sur culture de cellules Vero, le vaccin vivant atténué et le vaccin chimère vivant ont tous un profil d'innocuité acceptable. Le suivi dans le cadre d'études post-homologation, importantes pour détecter les événements indésirables rares, reste limité pour certains des produits les plus récents. Les données limitées disponibles sur l'administration concomitante du vaccin antirougeoleux ou du vaccin antirougeoleux-antiourlien-antirubéoleux ne révèlent aucune interférence pour ce qui est de l'innocuité et de l'immunogénicité et confortent cette pratique dans le cadre de la vaccination systématique ou des campagnes de vaccination, mais de nouvelles études sont souhaitables, notamment avec d'autres vaccins à valence rougeole et les vaccins contre la varicelle.

Le SAGE a conclu que la vaccination contre l'EJ devait être étendue à toutes les régions où cette maladie est reconnue comme une priorité de santé publique. Même si le nombre des cas confirmés est faible, du fait des difficultés rencontrées pour la surveillance et pour documenter les cas, on envisagera cette vaccination dès qu'on est en présence d'un environnement convenant bien à la transmission de l'EJ (c'est-à-dire la présence de réservoirs animaux, des conditions écologiques favorables à la transmission du virus et la proximité avec d'autres pays ou régions où la transmission est avérée), si une charge de morbidité importante est plausible. Comme l'EJ est transmise par les moustiques et se maintient grâce à un cycle enzootique, la vaccination ne protège que les sujets vaccinés. Comme elle n'aboutit pas à la constitution d'une immunité de groupe, il est nécessaire d'avoir une couverture vaccinale élevée. Les données factuelles à notre disposition démontrent un impact limité des stratégies autres que la vaccination, comme la lutte antivectorielle, et il n'est donc pas conseillé de détourner les moyens consacrés à la vaccination au profit de ces autres interventions.

Le SAGE a réaffirmé qu'il est hautement prioritaire de recueillir des données sur l'échec de la vaccination afin d'être informé sur le besoin éventuel d'administrer des doses de rappel, susceptible de varier en fonction des vaccins et de la situation de la transmission. Il faut renforcer la surveillance pour évaluer le fardeau de l'EJ, orienter les stratégies de vaccination, identifier les cas chez les sujets vaccinés, surveiller l'innocuité des vaccins afin de repérer d'éventuels événements indésirables rares, et suivre l'impact et l'efficacité des vaccins contre l'EJ. Il est nécessaire de mettre au point des réactifs standardisés pour les essais de neutralisation, afin de garantir la disponibilité de tests sérologiques sensibles, spécifiques et financièrement abordables dans le commerce pour la réalisation de tests dans les pays d'endémie.

Meningococcal A conjugate vaccine

SAGE was requested to consider the preferred schedules for meningococcal A conjugate vaccine for infants and young children living in the African meningitis belt countries, in order to achieve sustainable disease control following initial mass vaccination campaigns targeting those aged 1–29 years. SAGE was informed by: (i) a progress update on the roll-out of the meningococcal A conjugate vaccine through mass vaccination campaigns in the African meningitis belt countries, where over 153 million people have been vaccinated in 12 of the 26 target countries, with overall high vaccine coverage estimates and major impact on disease incidence and carriage, as well as preliminary economic impact assessments indicating significant cost savings for households and health systems; (ii) a summary of results from clinical trials of immunogenicity and safety among infants and young children [2 studies conducted in Ghana (dose ranging, 1-dose and 2-dose infant schedules, vaccine co-administration, immune persistence and safety) and in Mali (confirmation of schedule and formulation, vaccine co-administration and safety)] and an overview of routine vaccine coverage data in the African meningitis belt countries; (iii) the results from transmission and disease mathematical modelling of group A *Neisseria meningitidis* designed to investigate strategies for the optimal long-term use of the meningococcal A conjugate vaccine; (iv) the results from a high quality observational study evaluating meningococcal A conjugate vaccine safety in pregnant women.

SAGE reiterated the importance of efforts to complete mass vaccination campaigns in all African meningitis belt countries. SAGE recommended that countries completing these campaigns should introduce the vaccine into the routine childhood immunization programme within 1–5 years following campaign completion, along with a one-time catch-up campaign for young children born since the initial mass vaccination who would be outside the age window when the routine immunization programme starts. SAGE considered that in areas where routine childhood vaccination coverage is <60% (the coverage estimated by models to result in herd immunity) periodic supplementary immunization activities could be considered as a mitigation strategy complementary to continuing routine vaccination, as indicated by ongoing surveillance.

SAGE concluded that the immunological evidence was sufficient to establish that a lower vaccine dosage (5 µg) can be recommended for vaccine given between 3 and 24 months of age and that for the routine immunization programme a 1-dose schedule for those aged ≥9 months is sufficiently immunogenic. Evidence was also presented for vaccination starting at 3 months of age in a 2-dose primary schedule. Given the high level of herd immunity following mass campaigns, the epidemiologic evidence on the age distribution of disease, and the programmatic and economic considerations, SAGE recommended a 1-dose schedule at ≥9 months of age. The single dose could be administered between 9 and 18 months of age based on local programmatic and epidemiologic considerations. If a child misses vaccination at the recommended age he/she should receive

Vaccin conjugué contre le méningocoque A

Il a été demandé au SAGE d'étudier les calendriers préférables d'administration du vaccin conjugué contre le méningocoque A chez les nourrissons et les jeunes enfants vivant dans les pays de la ceinture africaine de la méningite, afin d'arriver à maîtriser durablement la maladie après les campagnes initiales de vaccination de masse ciblant les personnes âgées de 1 à 29 ans. Le SAGE s'est informé avec: i) un rapport sur les progrès accomplis dans le déploiement du vaccin conjugué contre le méningocoque A dans le cadre de campagnes de vaccination de masse dans les pays de la ceinture africaine de la méningite, où >153 millions de personnes ont été vaccinées dans 12 des 26 pays ciblés, avec dans l'ensemble des estimations élevées de la couverture vaccinale, un impact majeur sur l'incidence et le portage de la maladie, ainsi que des évaluations préliminaires de l'impact économique révélant des économies substantielles pour les ménages et les systèmes de santé; ii) une synthèse des résultats des essais cliniques sur l'immunogénicité et l'innocuité chez les nourrissons et les jeunes enfants [2 études faites au Ghana (évaluation du dosage, calendriers à 1 ou 2 doses chez le nourrisson, administration concomitante avec d'autres vaccins, persistance de l'immunité et innocuité) et au Mali (confirmation du calendrier et de la présentation, administration concomitante avec d'autres vaccins et innocuité)] et une vue d'ensemble des données de la couverture vaccinale dans les pays de la ceinture africaine de la méningite; iii) les résultats de la modélisation mathématique de la transmission et de la maladie pour *Neisseria meningitidis* du groupe A, conçue pour étudier les stratégies concernant l'utilisation optimale du vaccin conjugué contre le méningocoque A sur le long terme; et iv) les résultats d'une étude observationnelle de grande qualité évaluant l'innocuité du vaccin conjugué contre le méningocoque A chez la femme enceinte.

Le SAGE a réaffirmé l'importance des efforts pour achever les campagnes de vaccination de masse dans l'ensemble des pays de la ceinture africaine de la méningite. Il a recommandé aux pays terminant ces campagnes d'introduire le vaccin dans les programme de vaccination systématique de l'enfant de 1 à 5 ans après la fin de la campagne, avec une campagne unique de rattrapage pour les enfants nés depuis la vaccination de masse initiale et se trouvant en dehors de la tranche d'âge concernée au démarrage du programme de vaccination systématique. Le SAGE a considéré que dans les régions où la couverture de la vaccination systématique des enfants est <60% (niveau qui, selon les estimations des modèles, confère une immunité de groupe), des activités de vaccination supplémentaires périodiques peuvent être envisagées comme une stratégie complémentaire d'atténuation en renfort de la poursuite de la vaccination systématique, selon ce qu'indique la surveillance continue.

Le SAGE a conclu qu'il y avait des preuves immunologiques suffisantes pour établir qu'un dosage plus faible (5 µg) peut être recommandé pour les vaccins administrés à un âge compris entre 3 et 24 mois et que, pour les programmes de vaccination systématique, un calendrier d'1 dose pour les enfants ≥9 mois est suffisamment immunogène. Des données probantes ont également été présentées pour une administration à partir de l'âge de 3 mois dans le cadre d'un calendrier de vaccination primaire à 2 doses. Compte tenu du niveau élevé de l'immunité de groupe après les campagnes de masse, des données épidémiologiques sur la répartition de la maladie selon l'âge, ainsi que des considérations programmatiques et économiques, le SAGE recommande un calendrier de vaccination d'une seule dose à un âge ≥9 mois. Celle-ci peut être administrée à un âge compris entre 9 et 18 mois selon les considérations programmatiques et épidémiologiques. Si un enfant n'a pas bénéficié de la vaccina-

a single dose as soon as possible thereafter. If in a specific context there is a compelling reason to immunize infants <9 months of age, a 2-dose priming infant schedule should be used starting at 3 months of age with doses at least 8 weeks apart, based on evidence from other polysaccharide-protein conjugate product data and immunologic principles. Data on simultaneous administration with other vaccines (i.e. co-administration), but at different anatomical sites, has been evaluated and found to be acceptable for diphtheria toxoid, tetanus toxoid, whole cell pertussis, hepatitis B, *Haemophilus influenzae* type b, oral poliovirus, yellow fever, measles and rubella vaccines. No evidence exists for co-administration with rotavirus, pneumococcal conjugate or inactivated polio vaccines. SAGE noted that there is no reason to expect vaccine interference and absence of data should not discourage co-administration.

tion à l'âge recommandé, il devra recevoir une dose unique dès que possible par la suite. Si dans un contexte spécifique il existe une raison impérieuse de vacciner les enfants avant l'âge de 9 mois, le calendrier de primovaccination à 2 doses sera appliqué à partir de l'âge de 3 mois et avec un intervalle d'au moins 8 semaines entre les 2 doses, en se fondant sur les principes de l'immunologie et sur les données factuelles obtenues avec d'autres produits conjugués à base de protéines et de polyosides. Les données sur l'administration simultanée avec d'autres vaccins (c'est-à-dire une administration concomitante), mais sur des sites anatomiques différents, ont été évaluées et se sont avérées recevables pour l'anatoxine diphtérique, l'anatoxine tétanique, le vaccin anticoquelucheux à germes entiers, le vaccin contre l'hépatite B, contre *Haemophilus influenzae* type b, le vaccin antipoliomyélitique oral et les vaccins contre la fièvre jaune, la rougeole et la rubéole. Il n'existe pas de données factuelles sur l'administration concomitante avec les vaccins antirotavirus, antipneumococcique conjugué et antipoliomyélitique inactivé. Le SAGE relève qu'il n'y a pas de raison de s'attendre à des interférences et que l'absence de données ne doit pas décourager l'administration concomitante de plusieurs vaccins.

SAGE concluded that vaccination of pregnant women is safe, as assessed in a high quality observational study and therefore pregnant women should continue to be included if in the age group targeted by mass vaccination campaigns.

Le SAGE a conclu que la vaccination est sûre chez les femmes enceintes, comme il ressort d'une étude observationnelle de grande qualité et que, donc, elles doivent toujours être incluses si elles font partie de la tranche d'âge ciblée par les campagnes de vaccination de masse.

SAGE endorsed the need for conducting long-term high quality surveillance and vaccine programme evaluation among meningitis belt countries, where possible, to: (i) document vaccine effectiveness, and impact on invasive disease and carriage; (ii) define reliable correlates of protection and duration of protection; (iii) determine whether booster doses are needed; (iv) monitor the evolving epidemiological situation for possible replacement disease due to other meningococcal serogroups, to refine policies and inform development of multivalent conjugate vaccines; (v) assess vaccine coverage and document safety; (vi) evaluate vaccination in special populations such as pregnant/lactating women and immunocompromised subjects; (vii) identify vulnerable groups through long-term follow-up of vaccine trial participants and serial seroprevalence studies; (viii) document the effect on immunity to tetanus given that tetanus toxoid is used to conjugate this vaccine; (ix) assess the economic impact on households and on health systems.

Le SAGE a confirmé le besoin de mener une surveillance de qualité sur le long terme et de procéder à une évaluation du programme de vaccination dans les pays de la ceinture de la méningite, si possible, pour: i) documenter l'efficacité du vaccin, ainsi que l'impact sur la maladie invasive et le portage; ii) définir des corrélations fiables de la protection et de la durée de celle-ci; iii) déterminer si des doses de rappel sont nécessaires; iv) suivre l'évolution de la situation épidémiologique pour voir une éventuelle substitution par des méningocoques appartenant à d'autres sérogroupes, pour affûter la politique et orienter la mise au point de vaccins conjugués multivalents; v) évaluer la couverture vaccinale et établir l'innocuité; vi) évaluer la vaccination dans des groupes particuliers de la population, comme les femmes enceintes/allaitantes ou les sujets immunodéprimés; vii) déterminer les groupes vulnérables au moyen d'un suivi de longue durée des participants aux essais des vaccins et de séries d'études sur la séroprévalence; viii) réunir des informations sur l'effet concernant l'immunité contre le tétanos, vu que ce vaccin conjugué est produit avec l'anatoxine tétanique; et ix) évaluer l'impact économique sur les ménages et sur les systèmes de santé.

Polio eradication

SAGE reviewed the readiness criteria for type 2 oral poliovirus vaccine (OPV2) withdrawal globally which include: (1) at least 1 dose of IPV in OPV-using countries; (2) bivalent oral polio vaccine (bOPV) licensed for routine immunization; (3) type 2 poliovirus surveillance and response protocols and monovalent OPV (mOPV) stockpile; (4) appropriate containment and handling of residual type 2 materials; and (5) verification of global eradication of wild poliovirus type 2.

SAGE confirmed that preparations for OPV2 withdrawal in early 2016 are on track and recommended that WHO Member States be formally apprised of this through WHO's governing bodies to accelerate preparations and facilitate international coordination.

Éradication de la poliomyélite

Le SAGE a examiné les critères de préparation au retrait mondial du vaccin antipoliomyélitique oral de type 2 (VPO2), à savoir: 1) l'administration d'au moins 1 dose de VPI dans les pays utilisant le VPO; 2) l'homologation du vaccin antipoliomyélitique oral bivalent (VPOb) pour la vaccination systématique; 3) la surveillance du poliovirus de type 2, des protocoles de riposte et des stocks de VPO monovalent (VPOm) en réserve; 4) le confinement et la manutention appropriés des matériels résiduels contenant du virus de type 2; et 5) la vérification de l'éradication mondiale du poliovirus sauvage de type 2.

Le SAGE a confirmé que les préparatifs pour le retrait du VPO2 début 2016 sont dans les temps et a recommandé que les États Membres soient officiellement informés par les organes directeurs de l'OMS pour accélérer la préparation et faciliter la coordination internationale.

SAGE endorsed the protocols for the management and use of the global mOPV2 stockpile and for type 2 poliovirus response in the post-OPV2 era, the plan for expansion of environmental surveillance, and the revised strategy for containment of polioviruses (i.e. the third edition of the WHO global action plan to minimize facility-associated risk in post-eradication/post-OPV era or GAP III). SAGE recognized and appreciated that countries with more than 95% of the global birth cohort, including almost all countries at highest risk for persistent type 2 circulating vaccine derived poliovirus (cVDPV2) emergence and circulation, either already use IPV or have formally expressed a commitment or intent to introduce IPV by end-2015. SAGE noted the current shortage in IPV supply but was reassured by the ongoing mitigation activities. SAGE further urged:

(a) accelerated licensure of bOPV for routine use and consideration of new regulatory approaches;
(b) utilization of global mOPV2 stockpiles only to manage post-cessation type 2 poliovirus; and
(c) completion of poliovirus containment phase 1 activities by end-2015.

SAGE reiterated its concern about continued persistent cVDPV2 circulation in Nigeria and Pakistan, and reinforced its previous recommendation (April 2014) that elimination of persistent cVDPV2 by mid-2015 at latest should have the same priority as elimination of wild polioviruses. SAGE concurred that Nigeria should schedule sufficient trivalent tOPV campaigns across the northern states to interrupt the circulation of cVDPV2 by March 2015. Nigeria should also consider the use of IPV, simultaneously with OPV, in campaigns targeting areas with low type 2 immunity. Pakistan should exploit the improved access in the north-west of the country to ensure that sufficient tOPV is used in all areas, especially for children from conflict-affected areas, and the judicious use of IPV, to interrupt persistent cVDPV transmission as soon as possible.

Lastly, SAGE endorsed the proposed risk-based approach for boosting immunity to type 2 poliovirus prior to OPV2 withdrawal, by ensuring that sufficient tOPV campaigns are planned and conducted to raise population immunity above the estimated threshold for transmission in areas at highest risk of cVDPV2 emergence. SAGE emphasized that planning for this risk-based approach should be done on a subnational basis.

Hepatitis E vaccine

The SAGE Hepatitis E Working Group report to SAGE included information on the hepatitis E virus (HEV) vaccine pipeline, the epidemiology and disease burden of hepatitis E, and the composition, safety, immunogenicity and efficacy of the hepatitis E vaccine licensed in China in 2011.

SAGE noted that every year an estimated 20 million HEV infections occur globally resulting in more than 3 million clinical cases and 70 000 deaths. Most cases

Le SAGE a approuvé les protocoles de gestion et d'utilisation des stocks mondiaux de VPOm2, ainsi que de riposte aux poliovirus de type 2 lors de la période après le VPO2, le plan d'extension de la surveillance de l'environnement et la stratégie révisée pour le confinement des poliovirus (c'est-à-dire la troisième édition du plan d'action mondial de l'OMS pour réduire au minimum le risque d'exposition au poliovirus associé aux établissements après l'éradication des poliovirus sauvages et l'arrêt de la vaccination systématique par le VPO, appelé GAP III). Le SAGE a reconnu et apprécié que les pays réunissant >95% de la cohorte mondiale de naissances, incluant presque tous les pays ayant le risque le plus élevé d'émergence et de circulation de poliovirus circulants dérivés d'une souche vaccinale de type 2 (PVDVc2), soit utilisent déjà le VPI, soit ont officiellement exprimé leur engagement ou leur intention de l'introduire d'ici fin 2015. Le SAGE a pris note de la pénurie actuelle de VPI mais a été rassuré par les actions en cours pour atténuer les problèmes d'approvisionnement. Il a de plus appelé instamment à:

a) accélérer l'homologation du VPOb pour un usage systématique et à envisager de nouvelles approches réglementaires;
b) utiliser uniquement les stocks mondiaux de VPOm2 pour gérer les poliovirus de type 2 apparaissant après l'arrêt du VPO2; et
c) terminer la phase 1 des activités pour le confinement des poliovirus d'ici fin 2015.

Le SAGE a rappelé son inquiétude concernant la circulation persistante de PVDVc2 au Nigéria et au Pakistan et a insisté sur sa recommandation précédente (avril 2014) d'accorder à l'élimination des PVDVc2 persistants d'ici la mi-2015 au plus tard la même priorité qu'à l'élimination des poliovirus sauvages. Le SAGE s'accorde pour dire que le Nigéria devrait programmer des campagnes suffisantes d'administration du VPOt dans les États du Nord pour interrompre la circulation des PVDVc2 d'ici mars 2015. Ce pays devrait également envisager l'utilisation du VPI, simultanément avec le VPO, dans le cadre de campagnes ciblant des zones où l'immunité contre le virus de type 2 est faible. Le Pakistan doit exploiter l'accès amélioré au nord-ouest du pays pour assurer l'utilisation de quantités suffisantes de VPOt dans toutes les régions, en particulier pour les enfants vivant dans des zones en proie à des conflits, et l'usage judicieux du VPI, afin d'interrompre le plus vite possible la transmission persistante de PVDVc.

Enfin, le SAGE a approuvé l'approche fondée sur le risque, proposée pour renforcer l'immunité contre les poliovirus de type 2 avant le retrait du VPO2, en veillant à ce que suffisamment de campagnes d'administration du VPOt soient planifiées et exécutées pour élever, dans les zones les plus exposées au risque d'émergence de PVDVc2, l'immunité des populations au-dessus du seuil qui, d'après les estimations, permet la transmission. Le SAGE a souligné que la planification de cette approche fondée sur le risque devait être faite au niveau infranational.

Vaccin contre l'hépatite E

Le rapport du groupe de travail du SAGE sur l'hépatite E comportait des informations sur la filière de recherche des vaccins contre le virus de l'hépatite E (VHE), sur l'épidémiologie de cette maladie et la charge de morbidité qui lui est due, ainsi que sur la composition, l'innocuité, l'immunogénicité et l'efficacité du vaccin anti-hépatite E homologué en Chine en janvier 2011.

Le SAGE a relevé qu'on estime à 20 millions le nombre d'infections à VHE se produisant chaque année dans le monde et qu'elles sont responsables de >3 millions de cas cliniques et

occur in developing countries where in addition to sporadic cases many small and occasional large scale outbreaks also occur. Hepatitis E case-fatality is highest among pregnant women, and can reach 20% when disease occurs in the third trimester of pregnancy. Outbreaks are frequent in Asia and Africa and result in high morbidity and mortality, particularly when occurring in displaced persons camps. Current understanding of HEV transmission indicates that effective prevention and control depend on ensuring safe drinking water, adequate sanitation and proper personal and environmental hygiene. However, in settings where hepatitis E outbreaks occur, it is difficult to mount adequate prevention measures in a timely manner, mainly due to rapid transmission of HEV and the long incubation period (15–60 days).

The only currently licensed hepatitis E vaccine, Hecolin®, is a recombinant vaccine which contains virus-like particles prepared using a recombinant *Escherichia coli* expression system. The vaccine is approved for use in China in those aged 16–65 years. Hecolin® is well tolerated and has been demonstrated to have a good safety profile in this age range.

Current evidence demonstrates that this vaccine is highly immunogenic, with nearly all the recipients seroconverting after 3 doses administered in a 0, 1 and 6 month schedule. Limited data show that even 2 doses (at 0 and 6 months, or at 0 and 1 month) lead to a high rate of seroconversion, though with lower antibody titres.

The vaccine protects against symptomatic HEV infection, with over 90% efficacy based on clinical trials involving 109 959 individuals. Data on protection are primarily applicable to genotype 4 associated disease; data on disease caused by other genotypes are too limited (genotype 1) or not available (genotype 2 and 3). The duration of follow-up in the available published reports has been for up to 2 years. In addition, unpublished data provided by the manufacturer show persistence of immunity for up to 4.5 years. Longer term efficacy, duration of protection, and the potential need and timing for booster doses remain to be determined.

Data on safety and efficacy in children aged <16 years or persons aged >65 years, and in areas with genotype 1, 2 and 3 HEV infections, are lacking. Data on the safety and efficacy of the vaccine in pregnant women are limited. The vaccine appears to be safe and immunogenic in hepatitis B carriers; whether this extends to persons with chronic liver disease needs further study. Data on immunogenicity and protective efficacy in immunosuppressed individuals are not available. The efficacy of the vaccine when administered in a post-exposure setting or in controlling disease outbreaks has not yet been studied. Data on these aspects would enable better assessment of the clinical and public health applications of this vaccine.

Based on this information SAGE assessed the hepatitis E vaccine as a promising vaccine showing high efficacy against hepatitis E disease in healthy subjects aged 16–65 years in China. However, data on the incidence of HEV infection and disease, and the latter's

de 70 000 décès. La plupart des cas surviennent dans les pays en développement où, en plus des cas sporadiques, on observe de nombreuses flambées épidémiques réduites ou, à l'occasion, de grande ampleur. Le taux de létalité imputable à l'hépatite E est le plus élevé chez la femme enceinte et il peut atteindre 20% lorsque la maladie est contractée au troisième trimestre de la grossesse. Les flambées sont fréquentes en Asie et en Afrique et entraînent un fort taux de morbidité et de mortalité, en particulier lorsqu'elles se produisent dans les camps de personnes déplacées. Selon les connaissances actuelles de la transmission du VHE, l'efficacité de la prévention et de la lutte passe par la fourniture d'une eau de boisson salubre, des services d'assainissement suffisants et une hygiène correcte, au niveau personnel comme à celui de l'environnement. Toutefois, dans les situations où des flambées d'hépatite E se produisent, il est difficile de mettre en place à temps des mesures de prévention suffisantes, principalement à cause de la transmission rapide du virus et de la durée prolongée d'incubation (15 à 60 jours).

Le seul vaccin contre l'hépatite E actuellement homologué, Hecolin®, est un vaccin recombinant contenant des pseudoparticules virales préparées à partir d'un système d'expression recombinant provenant d'*Escherichia coli.* Son utilisation est homologuée en Chine pour les personnes âgées de 16 à 65 ans. Il est bien toléré et on a mis en évidence qu'il avait un bon profil d'innocuité dans cette tranche d'âge.

Les données actuelles montrent que ce vaccin est fortement immunogène, la séroconversion se produisant chez pratiquement tous les sujets vaccinés selon un calendrier de 3 doses sur 6 mois (mois 0, 1 et 6). Des données limitées indiquent que même 2 doses (administrées aux mois 0 et 6, ou 0 et 1) produisent un taux élevé de séroconversion, mais avec des titres plus faibles en anticorps.

Le vaccin protège contre l'infection symptomatique à VHE, avec une efficacité supérieure à 90% d'après des essais cliniques portant sur 109 959 personnes. Les données sur la protection s'appliquent principalement à la maladie associée au génotype 4; les données sur la maladie provoquée par d'autres génotypes sont trop limitées (génotype 1) ou ne sont pas disponibles (génotypes 2 et 3). La durée du suivi dans les rapports qui ont été publiés s'étend jusqu'à 2 ans. De plus, des informations non publiées fournies par le fabricant indiquent une persistance de l'immunité pouvant atteindre 4,5 ans. Il reste à déterminer l'efficacité sur le plus long terme, la durée de la protection, la nécessité potentielle de doses de rappel et le moment où il faut les administrer.

Les données sur l'innocuité et l'efficacité chez l'enfant de <16 ans ou la personne âgée de >65 ans, ainsi que dans les zones où sévissent des infections par des VHE des génotypes 1, 2 et 3 manquent. Celles sur l'innocuité et l'efficacité du vaccin chez la femme enceinte sont limitées. Il semble qu'il soit sûr et immunogène chez les porteurs du virus de l'hépatite B; il est en revanche nécessaire d'étudier de manière plus approfondie si cela s'applique aussi chez les personnes ayant une affection chronique du foie. On ne dispose pas de données sur l'immunogénicité et l'efficacité protectrice chez les sujets immunodéprimés. L'efficacité du vaccin lorsqu'il est administré en situation de postexposition ou pour endiguer des flambées n'a pas encore été étudiée. Des renseignements sur ces aspects permettraient de mieux évaluer les applications de ce vaccin au niveau clinique et pour la santé publique.

Sur la base de ces informations, le SAGE a estimé que le vaccin contre l'hépatite E était prometteur, démontrant une grande efficacité contre l'hépatite E chez les sujets sains âgés de 16 à 65 ans en Chine. En revanche, les données sur l'incidence de l'infection par le VHE et la maladie qu'il provoque, ainsi que

contribution to mortality in the general population in countries where infection is common, are quite limited.

SAGE concluded that without additional data, at this stage it is not possible to make any recommendation concerning the introduction of this vaccine in routine national programmes in populations where epidemic and sporadic hepatitis E disease is common. However, national authorities may decide to use this vaccine based on the local epidemiology.

The lack of sufficient information at this time does not allow SAGE to recommend the routine use of the vaccine for the following population sub-groups: children aged <16 years, pregnant women or women of childbearing age living in areas where hepatitis E disease is common, chronic liver disease patients, persons on an organ transplant wait-list, and travellers from low-endemicity areas to high-endemicity areas.

SAGE recognized that there could be special situations where the risk of serious morbidity and mortality is particularly high, and the lack of sufficient data at this point should not preclude the use of this vaccine in these special situations. In particular, SAGE emphasized that the use of the vaccine during outbreaks of hepatitis E should be considered.

In all the situations where hepatitis E vaccine is administered, experience with the use of vaccine, including the occurrence of any adverse events, should be documented. SAGE also recommended the pre-emptive design of research protocols that would examine the safety and effectiveness of the vaccine in a large-scale outbreak and generation of data in pregnant women.

Vaccine hesitancy

The SAGE Vaccine Hesitancy Working Group reported on its deliverables including: (i) the definition of vaccine hesitancy; (ii) hesitancy models and matrix of determinants; (iii) results of a survey of country immunization managers; (iv) hesitancy indicators; (v) tools and strategies to address vaccine hesitancy; and (vi) conclusions and recommendations. The group emphasized that the field of vaccine hesitancy is complex and rapidly evolving and that the deliverables reflect the current evidence. Potentially promising tools are under development but there is a need for standardization and validation of tools and monitoring and sharing of (evidence-based) best practices.

SAGE endorsed the definition of hesitancy: "Vaccine hesitancy refers to delay in acceptance or refusal of vaccines despite availability of vaccination services. Vaccine hesitancy is complex and context specific varying across time, place and vaccines. It includes factors such as complacency, convenience and confidence."

SAGE acknowledged that vaccine hesitancy may be present in situations where low vaccine uptake is occurring due to poor availability, lack of offer or access to vaccines, unfeasible travel distances to clinic, and poor programme communication but was not the priority to address in these situations. Vaccine hesitancy can be described by a matrix of contextual influences, individual/social influences, and vaccine and vaccination-specific issues.

la contribution de cette dernière à la mortalité dans la population des pays où l'infection est courante, sont assez limitées.

Le SAGE a conclu qu'en l'absence de données supplémentaires à ce stade, il était impossible de faire une recommandation sur l'introduction de ce vaccin dans les programmes nationaux de vaccination systématique dans les pays où des épidémies et des cas sporadiques d'hépatite E sont courants. Toutefois, les autorités nationales pourront décider d'utiliser ce vaccin sur la base de l'épidémiologie locale.

Il n'y a pas suffisamment d'informations pour l'instant pour permettre au SAGE de recommander l'utilisation systématique du vaccin dans les sous-groupes suivants de la population: les enfants de <16 ans, femmes enceintes ou en âge de procréer vivant dans des régions où l'hépatite E est courante, personnes atteintes d'une affection chronique du foie, personnes en attente d'une transplantation et voyageurs partant d'une zone de faible endémicité vers une zone de forte endémicité.

Le SAGE reconnaît qu'il peut y avoir des situations spéciales où le risque de morbidité grave et de mortalité est particulièrement élevé et l'insuffisance des données pour l'instant ne devrait pas empêcher d'utiliser le vaccin dans ce cas. Il souligne en particulier qu'on doit considérer son utilisation lors des flambées épidémiques d'hépatite E.

Dans toutes les situations où l'on administre le vaccin contre l'hépatite E, il faut enregistrer les informations sur cette expérience, y compris la survenue de tout effet indésirable. Le SAGE a également recommandé un modèle de protocoles de recherche anticipant les événements, examinant l'innocuité et l'efficacité du vaccin au cours d'une flambée épidémique de grande ampleur et générant des données pour les femmes enceintes.

Réticences à l'égard des vaccins

Le groupe de travail du SAGE sur l'hésitation à l'égard des vaccins a fait un rapport sur les résultats qu'il devait délivrer, à savoir: i) la définition du phénomène; ii) les modèles de réticence et une grille des déterminants; iii) les résultats d'une enquête auprès des administrateurs nationaux de la vaccination; iv) les indicateurs de réticence; v) les outils et stratégies pour remédier au problème; et vi) les conclusions et les recommandations. Le groupe a souligné qu'il s'agit là d'un domaine complexe, qui évolue rapidement, et que ces résultats traduisent l'état actuel des données factuelles. Des outils potentiellement prometteurs sont en cours de mise au point, mais il est nécessaire de les standardiser et de les valider ainsi que de suivre et de partager les meilleures pratiques (fondées sur des données probantes).

Le SAGE a approuvé la définition de l'hésitation: «Par hésitation à l'égard des vaccins, on entend le retard dans l'acceptation ou le refus des vaccins malgré la disponibilité de services de vaccination. C'est un phénomène complexe, spécifique au contexte et variant selon le moment, le lieu et les vaccins. Il inclut certains facteurs comme la sous-estimation du danger, la commodité et la confiance».

Le SAGE a reconnu que les réticences à l'égard des vaccins pouvait exister dans des situations où l'acceptation est faible en raison d'une disponibilité insuffisante, de l'inexistence de l'offre ou de l'accès aux vaccins, de distances insurmontables pour se rendre aux dispensaires et d'une mauvaise communication de la part du programme, mais que la priorité n'était pas de résoudre ce type de situations. On peut décrire les réticences à l'égard des vaccins au moyen d'une grille d'influences liées au contexte, à l'individu, au milieu social, ainsi qu'à certains aspects spécifiques des vaccins et de la vaccination.

The results from the 2013 survey of 13 immunization programme managers from the 6 WHO Regions found that the impact of vaccine hesitancy on vaccine uptake varied by country. Nevertheless, vaccine hesitancy was a concern in all countries and 8 undertook interventions to address it.

SAGE supported the use of the revised hesitancy indicators in the revised WHO/UNICEF Joint Reporting Form. One indicator focuses on reasons for vaccine hesitancy while the other focuses on the proportion of countries that have assessed the level of hesitancy in vaccination at a national or subnational level.

SAGE encouraged 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.

The Tailoring Immunization Programme of the WHO European Region is one of a number of potentially promising tools to diagnose barriers and design evidence-informed responses. SAGE applauded the tool though stated the need to have it modified and evaluated in various settings including low and middle income countries. Sharing of successes, failures, and lessons learnt across regions and globally is required. No single intervention strategy addresses all instances of vaccine hesitancy, though a systematic review found that dialogue-based, directly targeted approaches can improve vaccine uptake, including engaging leaders, social mobilization, mass media, improving convenience, reminders, training for health-care workers, and increasing awareness. Strategies that need further exploration include immunization pain mitigation and vaccine education for children and adolescents.

Consultation of marketing and communication experts indicated that focusing on benefits of immunization, drawing on emotional values, focusing on 1 or 2 key messages, employing proactive messaging, and using World immunization week as a global branding opportunity were important approaches to addressing hesitancy.

SAGE underlined the importance of distributing the matrix of determinants, the definition of hesitancy and the other deliverables to countries and partners.

SAGE endorsed the recommendations to WHO/UNICEF and other partners, and the recommendations to member states and regional and national immunization technical advisory groups.

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. ■

Les résultats de l'enquête de 2013 auprès de 13 administrateurs de programmes de vaccination dans les 6 Régions de l'OMS ont établi que l'impact de l'hésitation sur l'acceptation des vaccins varie selon les pays. Néanmoins, le phénomène est source de préoccupation dans tous les pays et 8 d'entre eux ont lancé des interventions pour y remédier.

Le SAGE est favorable à l'emploi, sur la nouvelle version de la fiche commune de déclaration OMS/UNICEF, d'indicateurs révisés pour les réticences. L'un d'eux s'intéresse aux motifs de l'hésitation à l'égard des vaccins tandis que l'autre porte sur le pourcentage de pays qui ont évalué l'ampleur du phénomène au niveau national ou infranational.

Le SAGE encourage la validation du compendium de questions d'enquête élaborées pour étudier les réticences à l'égard des vaccins, qui ont été évaluées et validées seulement dans certains pays à revenu élevé.

Le Programme d'adaptation de la vaccination de la Région OMS de l'Europe (Tailoring Immunization Program) est l'un des nombreux outils potentiellement prometteurs pour déceler les obstacles et concevoir des actions fondées sur des données factuelles. Le SAGE a fait l'éloge de cet outil mais a énoncé le besoin de le modifier et de l'évaluer dans diverses situations, y compris dans les pays à revenu faible ou intermédiaire. Il est nécessaire de partager les succès, les échecs et les enseignements tirés dans les différentes régions et à l'échelle mondiale. Aucune stratégie d'intervention ne peut à elle seule répondre à tous les cas de réticences à l'égard des vaccins, bien qu'un examen systématique ait constaté que des approches directement ciblées et basées sur le dialogue peuvent améliorer l'acceptation des vaccins: engagement des responsables, mobilisation sociale, intervention des médias, amélioration de la commodité, rappels, formation des agents de santé et sensibilisation. Certaines stratégies doivent être davantage étudiées comme l'atténuation de la douleur engendrée par la vaccination et l'éducation des enfants et des adolescents.

Il ressort d'une consultation avec des experts du marketing et de la communication que des méthodes importantes pour lever l'hésitation consistent à insister sur les avantages de la vaccination, à faire appel aux valeurs émotionnelles, à se concentrer sur 1 ou 2 messages essentiels, à instaurer une messagerie anticipative et à se servir de la Semaine mondiale de la vaccination comme d'un élément phare de promotion mondiale.

Le SAGE a souligné l'importance de distribuer la grille des déterminants, la définition de l'hésitation à l'égard des vaccins et d'autres résultats aux pays et aux partenaires.

Il a approuvé les recommandations destinées à l'OMS/l'UNICEF et à d'autres partenaires, ainsi que celles pour les États Membres et les groupes consultatifs techniques nationaux de la vaccination.

Le SAGE a reconnu la nécessité de développer des capacités de base au niveau du Siège et des Régions pour obtenir des connaissances sur les comportements pouvant être appliquées de manière intégrée dans le domaine de la prévention, qu'il s'agisse de nombreuses maladies transmissibles, non transmissibles ou de réticences à l'égard des vaccins. Cela supposera la participation de sociologues, de psychologues, d'anthropologues, d'experts du marketing social, de la communication, ainsi que de spécialistes des maladies et vaccins spécifiques. ■

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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	A recommendation was made for consideration of a platform for immunization coverage in the 2nd year of life, in view of potential necessary booster doses and opportunities to catch up with incomplete vaccination, and removing the artificial barrier often experienced after the 1st birthday.	Apr 2014	Ongoing	The proposal to the Bill and Melinda Gates Foundation (BMGF) was successful, and the Working Group (WG) is being put together at this time. Two pilot countries are being identified to review their experience with the establishment of a vaccination visit in the second year of life, and to propose strategies to improve on these visits. This will be used in the next two years to develop generic guidance to countries wishing to establish such a visit.
General	SAGE encouraged the Regional Office in EMRO to pay special attention to countries affected by political turmoil and requested specific monitoring for any adverse impacts on immunization programmes in GAVI graduating countries.	Apr 2011	Ongoing	There are no GAVI graduating countries in the Eastern Mediterranean Region (EMR). EMRO is working closely with and is paying special attention to the countries affected by political turmoil. The following support was provided since the last SAGE meeting in October 2014: • Egypt: Provision of technical support to Ministry of Health (MOH), Egypt, for controlling measles outbreak and planning outbreak response supplemental immunization activities (SIAs). Preparing proposal for inactivated polio vaccine (IPV) introduction utilizing Polio support to non GAVI countries • Jordan: continuing implementation of routine vaccination in the provinces hosting the refugees camps in Jordan. • Iraq: implementation of the national Measles campaign, reviewing EPI schedule and improving vaccine procurement in Iraq • Syria: Conducting comprehensive Expanded Program on Immunization (EPI) review, including data quality assessment and effective vaccine management assessment • Libya: Planning for priority areas for supporting EPI in Libya in 2015 • Yemen: Supporting implementation of measles/rubella MR campaign and 2 rounds periodic intensification of routine immunization (PIRI) in the low coverage governorates
General	SAGE recommended that ways to improve curricula for medical personnel should be explored.	Nov 2008	Ongoing	A workshop organized by WHO/AFRO (African Regional Office) was held in Grand Bassam (Cote d'Ivoire) from 13-17 May 2013, in collaboration with the Ministry of Health MOH and other immunization partners (GAVI, UNICEF, United States Agency for International Development USAID/Maternal and Child Health Integrated Program MCHIP and Network for Education and Support in Immunisation NESI) to revise the 2006 EPI (Expanded Program on Immunization) prototype curricula for medical & nursing/midwifery teaching schools in the African Region of WHO (AFR). During the workshop, 4 drafts of EPI prototype curricula were produced and were to be harmonized, finalized and edited. That is 2 curricula for medical schools in French and 2 curricula French & English for nursing/midwifery schools. The 4 curricula will be finalized during a meeting in AFR to review the pre service curriculum and AFRO mid level manager (MLM) modules (April 6-16, 2015).
General	SAGE called for the identification of novel communication strategies for the work of GACVS to have a greater impact and help maintain confidence in vaccines.	Apr 2014	Ongoing	A document on the Global Advisory Committe on Vaccine Safety (GACVS) future is currently under preparation and will address this issue in particular. The final draft should be submitted by mid-April 2015 to a peer-reviewed journal.

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General	SAGE encouraged the European region to document and share its experiences in country profiling, tailoring responses and using novel communication strategies to effect behaviour change.	Nov 2010	Ongoing	WHO European Regional Office (EURO) is working to support countries in addressing vaccine hesitancy at the individual and community levels, in building risk and crisis communication capacity, in strengthening resource mobilization and advocacy capacity, and in using behavioural insights methodologies to tailor programme delivery and to drive demand for vaccines. This includes activities in the following areas: 1. Application of the Tailoring Immunization Programs "TIP" toolkit, which allows a country or sub-national level authorities to segment/profile a population based on behaviors rather than background characteristics. The resulting group profile can help inform programmatic responses that could be communication-oriented or inform improved service delivery. Best practices from other disease programs are included that can be adapted for country-specific issues. Pilot testing of the framework has been conducted in several European countries: TIP was implemented in Bulgaria and on three projects in Sweden (Somali immigrants, migrants, and anthroposophic communities) and Bulgaria in 2013, and in the UK, Kazakhstan and Germany in 2014. In partnership with Wits University in South Africa, TIP is being adapted for use on a global level and a second edition (LIC, low income country, field guide) to be published towards the end of 2015. 2. Strengthening the ability of Member States to handle crises in vaccine confidence and trust through a guidelines document on vaccine safety communication, which was published in 2013. In 2014, 13 countries received exercise/simulation-based training on managing the communications response to vaccine safety events. 3. A resource mobilization and immunization advocacy workbook has been developed and will be launched region-wide in English and Russian languages during European Immunization Week (April 20-24). Subsequent sub-regional training sessions are planned in June and October 2015. 4. A vaccine communications review methodology has been developed by EURO and has been applied in 2 Member States in 2014 and in Montenegro and Moldova in 2015. An additional review is planned to take place in the Russian Federation later in 2015. 5. A vaccines social media strategy has been launched. A vaccination reminder 'app' for smart phones has been developed and country versions have been launched in 4 Member States with others due to launch in European Immunization Week 2015. 6. An online vaccines resource centre was launched in 2012 and has been strengthened and improved through 2013-14, with a number of member states using or translating the caregiver and health-care worker tools presented. 7. In early 2015 work continues on developing the school-based learning module on vaccines and immunization – drawing on a 'flipped learning' methodology – with children aged 8-10 learning with parents at home and reinforcing understanding in the classroom setting.
General	SAGE recommended strengthening national vaccination programs, integrating health services and strengthening health systems to promote universal health coverage.	Apr 2013	Ongoing	A teleconference was held 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 Program on Immunization (EPI) is working on. Subsequently, in early June a draft typology was produced and shared that summarizing this area of work. It was agreed that an effort would be made to highlight this area of work in a few slides of the WHO Department of Immunization, Vaccines and Biologicals (IVB) Director's next presentation to SAGE. Discussions are ongoing. The topic was discussed at the April 2014 SAGE meeting. SAGE concluded that addressing integration, by its very nature, requires a broader discussion beyond SAGE. In this regard, it was proposed that the SAGE working group on the Decade of Vaccines (DoV) consider options for moving forward, as integration is reflected as both a guiding principle and a strategic objective of the Global Vaccine Action Plan (GVAP). The Department secured funding at the end of 2014 to establish a position dedicated to the issue of integration. The recruitment is underway and should be completed during April 2015 and the position filled by the summer. We will report at the October 2015 SAGE on progress made with activities in this area.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
General	SAGE requested that a paper be developed, highlighting the circumstances under which off-label use of any vaccine can be recommended, while clarifying the differences between regulatory decisions and public health recommendations. Legal and programmatic implications of off-label recommendations and the need for clear communication should be considered.	Apr 2012	Ongoing	Advice being sought through the Expert Committee on Biological Standardization (ECBS) - added to agenda of next meeting, 15-19 October 2012. SAGE had previously requested that a paper be developed, highlighting the circumstances in which off-label use of any vaccine could be recommended, while clarifying the differences between regulatory decisions and public health recommendations. During the November 2012 SAGE meeting, SAGE further requested that ECBS prepare guidance for national regulatory authorities on studies needed to support evidence-based, off-label use of vaccines which benefit public health. It was noted that for regulators, product specific data are paramount. SAGE requested that an additional document 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. The ECBS guidance document has been delayed and will be prepared after its October 2014 meeting. A paper clarifying the differences between regulatory decisions and public health recommendations has been commissioned. Following much delay, this paper intended for publication in a peer reviewed journal should be available for submission prior to the April 2015 SAGE meeting.
Accessibility of affordable vaccines: gaps and WHO's role in supporting emerging manufacturers	SAGE suggested to monitor gaps and opportunities and consecutively develop a systematic process to responds to these needs in collaboration with key partners. A perspective is to be presented at a future SAGE meeting on accessibility of affordable vaccines.	Nov 2010	Ongoing	WHO is actively contributing to increasing global access to vaccines through the following activities: 1) close collaboration (participation in annual meetings and bilateral meetings) with International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and Developing Country Vaccine Manufacturer Network (DCVMN) as federations of manufacturers form developing and industrialized countries to ensure that they all have clarity on the needs of developing countries both in terms of types of vaccines but also in terms of their programmatic suitability; 2) Active participation in the annual DCVMN meeting to update them on new developments, concerns, and issues related to vaccine presentations, prequalification, regulation financing and priority country need. 3) WHO has resurrected and chaired the VPPAG (Vaccines Presentations and Packaging Advisory Group) a forum for discussion between the public and private sectors on the characteristics of vaccines required for developing countries. The full participation of industry enables them to have more visibility of the needs and constraints of countries; 4) The Decade of Vaccines (DoV) work stream on global access and vaccine price indicator which gets reported every years to the SAGE working group on the DoV. 5) General discussions on the process of technology transfers are taking place under the leadership of the Evidence Information and Research Cluster. 6) A new committee known as the Product Development for Vaccines Advisory Committee was established and met for the first time 8-10 Sep 2014. The group reviewed 19 pathogen specific global pipeline analyses (all available from the meeting website) and advised WHO on strategic prioritization for WHO activities related to early stage vaccine R&D (pre-licensure to Phase 2). The group will oversee the development of Vaccine Preferred Product Characteristics. 7) the Vaccine Product, Price and Procurement project (V3P) to support GAVI graduating and middle income countries through the provision of improved vaccine product and price information for decision-making. More information on V3P is provided under the topic of financing in the tracking sheet. 8) A Task Force on Middle Income Countries (MIC) has been established. More information on this is also provided elsewhere in the tracking sheet.
Childhood mortality	SAGE noted the recommendation by IVIR-AC that WHO would encourage countries to collect local data at country level and not only estimated age specific mortality rates by epidemiological modeling or expert elicitation.	Nov 2010	Ongoing	All models reviewed by the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) are hampered by the lack of primary data, and more efforts should be made to make such data readily available. Specifically, for pertussis disease burden estimation, IVIR-AC suggests validating the parameter estimates against data from Senegal and Europe as a first step, although primary data from developing countries that is currently not publicly available would provide a more compelling comparator for validation. For polio more primary data should be made available for all models. IVIR-AC recommends that polio related data should be made available for multiple modeling groups to encourage comparison of results using different approaches.Ongoing/standing issue for many other diseases.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Decade of vaccines/GVAP	The SAGE working group should continuously review the need for reformulation of the indicators or mechanisms for collection and reporting of data.	Nov 2012	Ongoing	The SAGE report of progress with the Global Vaccine Action Plan (GVAP) was presented to the WHO Executive Board (EB) on January 26, 2015. Twenty seven speakers made interventions. The report was very well received and the recommendations were uniformly welcomed. EB members highlighted several areas that required special attention. A meeting of the Working Group (WG) was held on March 11-13, 2015 to start preparations for the 2015 report.
Decade of vaccines/GVAP	SAGE also recognized the urgency for having approximate cost and impact estimates and recommended that the technical group provide preliminary estimates for SAGE review in November 2013.	Nov 2012	Completed	IVIR-AC (Immunization and Vaccines related Implementation Research Advisory Committee) concluded that the Decades of Vaccine (DoV) study presented on the approximate cost and impact may be adequate for high level use such as tracking of the Global Vaccine Action Plan (GVAP) and justifying its funding to donors on return of investment but had observations with the regard to the state of the art of the individual modeling components. Furthermore, IVIR-AC identified the need for increased transparency and clarity in all methods used including refined sensitivity and uncertainty analysis.
Dengue	A SAGE dengue working group should be convened to revise the data and prepare recommendations to SAGE as clical trial data is expected to be submitted to the regulatory authorities in early 2015.	Oct 2014	Ongoing	The SAGE Working Group on Dengue Vaccines has been constituted and will hold its first teleconference on March 31, 2015. The SAGE session for decision is still planned for April 2016.
Dengue Vaccine	SAGE requested that future recommendations on dengue vaccine safety be linked to the dengue vaccine development strategy.	Apr 2012	Ongoing	The dengue vaccine safety profile will be updated once an application for licensure has been filed. The Global Advisory Committee for Vaccine Safety (GACVS) will review the company's risk management plan at its June 2015 meeting.
Ebola	SAGE was asked to immediately establish a SAGE working group on Ebola vaccines and vaccination.	Oct 2014	Ongoing	The working group (WG) was established and has met three times via teleconference. A face-to-face meeting of the WG took place on March 9 and 10, 2015. The WG reviewed the current epemiological 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 will be presented to SAGE at the April 2015 meeting.
Global vaccine safety Blueprint	The Blueprint implementation should be led by WHO and its partners. It should be aligned with other related WHO capacity-building efforts. This includes in particular immunization programme and national regulatory authorities strengthening together with the development of national expert advisory bodies. SAGE suggested that a mechanism be developed to enable prioritization of both activities and countries in the implementation of the Blueprint. SAGE invited the GAVI Alliance and other partners to support this implementation.	Nov 2011	Ongoing	The Global Vaccine Safety Initiative (GVSI) has been launched. Its portfolio of activities is now publicly available covering all 8 strategic objectives with priorities endorsed by the Planning Group. The GVSI has been operating with 2 annual Planning Group meetings. It hosted its second annual meeting in November 2013. The third GVSI meeting took place in October 2014 in China, jointly with the national pharmacovigilance centres meeting.
GVAP	The Director-General of WHO should convene a special session at the 2015 World Health Assembly for countries with routine vaccination (DTP3) coverage of less than 80%, to which each Minister of Health will be asked to report on their challenges, plans and timelines to improve coverage to meet the GVAP goals. In addition the SAGE's GVAP assessment reports should remain as standing items at the WHA until 2020.	Oct 2014	Ongoing	The Director has called for a meeting of the heads of the technical units at the partner agencies to discuss a coordinated and cohesive response to the recommendations in the SAGE GVAP (Global Vaccine Action Plan) Assessment Report, including the selection of countries and the objectives, expected outcomes, and format for the meeting to be held during the World Health Assembly (WHA) 2015. Sponsorship has been submitted from 2 member states for a side meeting during the WHA 2015; final decision from governing bodies secretariat at WHO expected soon.

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	Post-market surveillance continues in Argentina and a detailed report on the recent epidemiological situation was provided to WHO in January 2015. In 2014 in the context of a localized outbreak in a border area, 8 potential breakthrough cases were identified. For 5 of them there is uncertainty about the vaccination status and/or conditions (cold chain) in which vaccination was administered. Seven of these cases are in the 5-9 age group (distributed throughout the period) and one in the 1-4 age group. This has resulted in an enhanced vigilance in the country. Currently, however, there is still no evidence of waning immunity and the situation is still compatible with very high vaccine effectiveness. The situation continues to be investigated. Hepatitis A cases have reached an all time low in 2013 and have remained low in 2014. As exemplified by the outbreak in San Martin there are the risk persists in the population. As also requested by SAGE, an economic analysis of the impact of the single dose immunization strategy against hepatitis A in Argentina has been done. Estimated total vaccination cost for the 2006-2010 post vaccination period was ~US$ 45 million. The total of medical and societal costs plus immunization cost decreased from ~US$ 105 million for 2000-2004(prevaccination) down to ~US$ 56 million for the 2006-2010 post vaccination period i.e. a reduction rate of 46.5%. Both Colombia and Paraguay also introduced a single dose national immunization schedule for 1 year old children. Yearly review of the Argentina surveillance data will continue.
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	EMRO: The Eastern Mediterranean Region (EMR) has a Regional Committee (RC) goal of reducing childhood hepatitis B prevalence to <1% among children <5 years by 2015. Its regional office, EMRO is working with Member States to ensure achievement of this goal. WPRO: The Western Pacific Region (WPR) established a Regional Committee goal to reduce hepatitis B infection to <1% among children at least 5 years of age by 2017. SEARO: The South East Asian Regional Office (SEARO) has a drafted regional strategy. AFRO: The African Regional Office (AFRO) has convened a regional hepatitis Technical Advisory Group (TAG) and plans to present a plan for comprehensive viral hepatitis control during the 2014 RC Meeting. In 2014, the AFRO Regional Committee meeting adopted resolution to reduce Hep B infection to <2% among children under 5 years of age by 2020. EURO: The European Regional Office (EURO) will consider a regional hepatitis B control goal. PAHO: The Pan American Health Organization (PAHO) has resolved to eliminate hepatitis B virus transmission and is formulating a regional strategy. Documenting the Impact of Hepatitis B Immunization: best practices for conducting a serosurvey (WHO/IVB/11.08) was published in 2011 by the department of Immunization, Vaccines and Biologicals. In 2012, WHO HQ has published a framework for global action to control viral hepatitis (http://www.who.int/csr/disease/hepatitis/Framework/en/index.html).

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Hepatitis B	SAGE recommended that the timely delivery of a birth dose of hepatitis B vaccine (that is, within 24 hours of birth) should be used as a performance measure for all immunization programmes. Reporting and monitoring systems should be strengthened to improve the quality of data on the birth dose.	Apr 2009	Ongoing	A consultation on implementation of new universal birth dose recommendation was conducted in December 2010 with special focus on countries with a high percentage of home births. Outputs include a monograph documenting the systematic review and best practices from the consultation. Immunization Practices Advisory Committee (IPAC) reviewed this work in early 2011 and again in April 2012, and endorsed the 2013 publication of 'Practices to Improve Coverage of the Hepatitis B birth dose vaccine'. From this, work is ongoing to develop field guidelines for scaling up Hepatitis B birth dose. The JRF (Joint Reporting Form) 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 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 counties to jointly propose actions towards improving birth dose uptake. In Jan 2015 the African Regional Office AFRO, and in March 2015 the WPRO, held Hep B birth dose consultations to improve birth dose coverages.
Hepatitis E	SAGE approved draft ToRs for a Working Group on Hepatitis E and requested that WHO establishes this group in the summer 2013.	Apr 2013	Completed	The SAGE Hepatitis E working group was established in 2013. The group met face-to-face in June 2014 and held multiple teleconferences. The group reported to SAGE at the October 2014 meeting and as a result of SAGE recommendations a WHO position paper on the use of hepatitis E vaccine has been finalized and will be published on May 1.
HIV	SAGE requested regular updates on the progress of HIV-vaccine research.	Apr 2010	Ongoing	There are now 3 major streams of HIV vaccine related research and development. Firstly follow-on to the RV144 Phase 3 trial in Thailand reported in 2009. Two follow-on Phase 3 trials of similar protein-poxvirus prime-boost approaches are planned in Thailand and South Africa. It was initially stated that the South African trial would start in 2015, although this has not been confirmed, and the start date may be deferred. Secondly there are several ongoing Phase 1-2 clinical trials of recombinant viral vectored approaches focusing on non Ad5 adenoviruses such as Ad26, Ad3, Ad35 and recombinant poxviruses such as MVA (Modified Vaccinia virus Ankara). Replicating vectored approaches (eg sendai virus) are also witnessing a renaissance in the global portfolio. 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 timeframe, but raise the prospect of cross-clade protection.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Immunization safety	SAGE encourages development of simple technological solutions with improved environmental characteristics, and encourages donors to support such work as a priority.	Nov 2007	Ongoing	- The WHO manual: Safe Management of Wastes from Health Care Activities second edition was published in 2013. http://apps.who.int/iris/bitstream/10665/85349/1/9789241548564_eng.pdf A series of 25 training modules for use in implementation of the manual and training health workers including waste handlers in the safe handling, treatment and disposal of health care waste has been completed. -Work is on-going through Project Optimize in collaboration with the Vaccine Packaging and Presentation Advisory Group (VPPAG) to explore vaccine packaging that minimizes the impact on environment. VPPAG has 2 related streams of work: 1) Developing recommendations to minimize primary, secondary, and tertiary container packaging, and 2) Drafting a consensus statement with industry about use of materials for vaccine packaging that will minimize environmental impact. - A document on Environmental due diligence procedures has been developed and shared with the Global Alliance for Vaccines and Immunizations (GAVI). It expresses steps to be taken to minimize and manage waste from immunization activities in an environmentally friendly manner. The WHO reference document is: WHO policy paper on Health Care Waste Management(see http://www.who.int/water_sanitation_health/medicalwaste/hcwmpolicy/en/index.html) - The health care waste component of Global Environment Facility (GEF) project is developing a small autoclave in Tanzania to treat waste produced in low income countries. The technology is ready and was launched at the final GEF meeting in December 2012 in Tanzania and is planned for use in a new GEF-funded project together with UNDP beginning in 2014 in four African countries: Ghana, Madagascar, Tanzania and Zambia. Replication of the design for scale-up in southeast Asia is in planning stages. - The issue of needle-cutters and WHO recommendation about their use have been in debate for at least 6 years now during every Safe Injection Global Network (SIGN) meeting. At the 2010 SIGN meeting, there was a special session on needle cutters. A Bangladesh study on the safety of using needle removers was reviewed. The results showed that hub cutters do not lead to increased needle-stick injuries among health care workers (HCWs). Based on the findings of this study, although there was no unanimity among the group, it was decided to state that WHO doesn't object (nor recommends) to the use of needle cutters, but their introduction should be associated with training HCWs on their use. A randomized controlled trial (RCT) on hub cutters has subsequently been completed in Ghana with WHO collaboration.
Immunization schedules	SAGE encouraged WHO to complete the project promptly. SAGE requested a critical appraisal of alternative schedules for pneumococcal conjugate vaccine, rotavirus vaccine and Hib vaccine in 2011.	Nov 2010	Ongoing	Pneumococcal Conjugate Vaccine (PCV): evidence was reviewed by SAGE on November 2011. New recommendation on schedules was issued and data was used to update the position paper. Rotavirus: evidence was reviewed by an ad-hoc group of experts in February 2012 and presented to SAGE in April 2012. An updated vaccine position paper on the use of rotavirus vaccines was published in February 2013. Haemophilus influenzae type b (Hib): The issue was revised during the April SAGE 2013 meeting. For all: review of number of contacts during first years of life (ongoing); cost of contacts (planned); update on actual age at vaccination data (completed and used in conjunction with rotavirus epidemiology). Completed for PCV, Rotavirus and Hib vaccines. Evidence on diphtheria-tetanus-pertussis (DTP) will be presented to SAGE in April 2015, with a focus on Pertussis. Evidence on Hep B vaccines will be presented in the October 2015 meeting - delays due to impact of Ebola outbreak.

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Immunization Supply Chains	SAGE recommended that the EVM assessment include the measurement of human resource capacity and encouraged WHO to use EVM assessments in alignment with new vaccine introduction impact assessments, to strengthen the links between supply chain issues and programme outcomes. To further improve the EVM assessment, it was suggested that the tool be used for supervisory purposes and that a composite score be developed to complement the across-the-board benchmark of 80%.	Apr 2014	Ongoing	Under the umbrella of the WHO-UNICEF Immunization Supply Chain and Logistics Hub, a process has started to developed a revised version of the Effective Vaccine Management (EVM) assessment tool for it to become an assessment that covers broader immunization supply chain and logistics aspects beyond vaccine management policies and practise. Since this is a significant undertaking and a time consuming one, the approach in 2015 will be to include additional data collection and/or assessment modules for Human Resources alongside the existing approach to EVM assessments. This Human Resource module is being developed by UNICEF Supply Division under the auspices of the People that Deliver (PtD) initiative and the Global Alliance for Vaccines and Immunizations (GAVI)People and Practise working group of the immunization supply chain taskforce. In addition, the revisions of the EVM assessment tool will include more supply chain performance measures and indicators that are more outcome oriented but aligned with the global key performance indicators being developed to track performance in countries with regards to the GAVI Supply Chain strategy.
Impact of the introduction of new vaccines on immunization and health systems	SAGE recommended that the ad-hoc working group work towards producing guidelines and tools for WHO to assist decision-makers and Expanded Program on Immunization (EPI) managers contemplating the introduction of new vaccines, in order to take account of collateral effects inherent in introduction. The guidelines should provide a set of indicators that would enhance the potential positive effects, and reduce any potential negative effects, both on the immunization system and the health system. The guidelines should accommodate vaccines with different characteristics. SAGE noted the importance of the ad hoc working group continuing to include a broad range of partner agencies, and encouraged to seek endorsement of this work at senior levels of partner agencies.	Apr 2010	Completed	Further information was collected through a search of the published, unpublished and grey literature (such as post-introduction evaluation reports), as well as through key informant interviews. An in-depth study in 7 countries was conducted by the London School of Hygiene and Tropical Medicine (LSHTM) in 2011-12 to gather further information. Final results were presented in a meeting in London in November 2013. The ad-hoc group has updated the framework based on the data obtained and has drafted a guideline (Vaccine Introduction Guidelines – Adding a vaccine to national immunization programme) to assist country decision makers and Expanded Program on Immunization (EPI) managers to take account of the potential effects/impacts of new vaccine introduction on the immunization and health systems. The 'Principles for adding a vaccine to a national immunization programme while strengthening the immunization and health systems' were endorsed by SAGE in April 2012 and form part of this guideline document, to be published in 2014. The ad hoc working group included a broad range of partner agencies (WHO, UNICEF, World Bank, Centre for Disease Control and Prevention CDC, PATH, John Snow Inc JSI, LSHTM, Johns Hopkins University JHU) and has sought endorsement of this work at senior levels of partner agencies. The revised Vaccine Introduction Guidelines (Principles and Considerations for Adding a Vaccine to a National Immunization Programme) which were published in 2014 as a result of the proceedings of the ad hoc working group, have been vetted by the partner agencies and endorsed by their senior personnel.
Implementation research	The implementation research agenda should define equity beyond traditional economic money metrics such as social economic status gradients, to include other measures of inequity such as the multidimensional poverty index or impacts on marginalized populations. SAGE suggested that studies to examine the integration of immunization with other health interventions should be included in the implementation research agenda.	Nov 2013	Ongoing	This recommendation is now part of the new Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) agenda under research to minimize barriers and improve coverage of vaccines currently in use. During the September 2014 meeting IVIR-AC identified the need for standardization of research tools and protocols to examine the integration of immunization with other health interventions and non-vaccination to be applied locally, by antigen including on how to translate the evidence to community messaging. IVIR-AC recommended to establish a sub-group to propose elements of the menu of solutions on the integration of care with immunization programs and another sub-group on non-vaccination. A two year time line selective approach on integration was proposed at two levels i.e. service delivery and management. IVIR-AC recommended to use the project proposal on "Evaluation of the Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD) interventions: example for Mazabuka District in Zambia" as a case study. As part of the Broader Social and Economic Value of Vaccines work portfolio in WHO several research proposals on this topic were suggested by a network of international researchers from academia, NGOs and decision makers during a ad-hoc WHO consultation in November 2014. Proposals were submitted for funding at Centres for Disease Control and Prevention (CDC)/Global Immunization Division (GID), the Global Alliance for Vaccines and Immunizations (GAVI), and Bill and Melinda Gates Foundation (BMGF). In March 2015, the "Impact of reaching hard to reach populations through routine immunization" proposal was awarded funding and has been started.

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Implementation Research	SAGE outlined some considerations for IVIR-AC to include in their deliberations – assessment of the use of high quality randomized controlled trials where feasible (noting the substantial ethical and methodological challenges involved), with sufficient power to explore sex differences, and a priori defined and standardized immunological endpoints designed to answer the specific question of non-specific effects– and emphasized that future research should draw on a broad investigator pool and from a wide range of geographic locations using a standardized protocol.	Apr 2014	Ongoing	During the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) September 2014 meeting, it was suggested to develop standardized protocols and start implementing high quality Randomized Controlled Trials (RCTs) where feasible. At least studies should mimic RCT situations with sufficient power to explore sex differences, and a priori defined and standardized immunological endpoints. With Bill and Melinda Gates Foundation (BMGF) support a multi-disciplinary team with IVIR-AC participation will start reviewing the evidence and identify research questions.
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	The September 2014 Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) meeting concluded that the models presented by modeling groups from Australia, UK and US were appropriate in terms of structure to better understand both schedule optimization in various countries and different transmission settings. However, availability and quality of data in low and middle income countries (LMICs) remains the key problem, thus IVIR-AC calls for better surveillance systems in LMICs. An IVIR-AC subgroup under the "WHO vaccine preventable diseases (VPD) burden and impact framework" will identify specific data needs for parameterization of various models by conjoining need with epidemiological expertise. Discussions are ongoing with modeling groups to discuss:) 1) Extending the models to high-mortality (i.e. low/middle-income) settings (including identifying data needs/gaps 2) Understanding the impact of differences in scheduling 3) Testing models with data from Colin Sanderson (London School of Hygiene and Tropical Medicine LSHTM) and the countries reviewed by the SAGE working group (WG). Preliminary results are expected to be presented at the upcoming IVIR-AC meeting in June 2015.
Influenza	SAGE requested that WHO report on epidemiology and surveillance of H7N9 as well as on the development of a potential vaccine candidate.	Apr 2013	Ongoing	Assessment of risk associated with avian influenza A(H7N9) remains unchanged. As of 1 Feb 2015, 486 cases have been confirmed with 185 deaths from China (Mainland, HK and Taiwan) including a Chinese case detected in Malaysia, and 2 cases with travel history to China reported from Canada. The majority of human cases are associated with exposure to infected live poultry or contaminated environments, including markets where live poultry are sold. A(H7N9) viruses seem circulating in poultry and their environments in the areas where human cases are occurring. Clinical and epidemiological features of H7N9 remain unchanged. So far the A(H7N9) virus antigenically are closely related to the WHO recommended vaccine virus A/Anhui/1/2013-like virus, although internal genes of the viruses are under constant reassortment with avian influenza A(H9N2) viruses endemic in poultry in parts of Asia. Several reverse-engineered high-growth reassortant candidate viruses are available for A(H7N9) vaccine development, though classical reassortment has not yet succeeded. WHO, through its global network, the Global Influenza Surveillance and Response System (GISRS), has been monitoring the evolution of the A(H7N9) and conducting continuous risk assessment.
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	Guide on Missed Opportunities for Vaccination (MOV) Assessment Methodology to be finalized by end of April 2015. Implementation of assessments are planned with AFRO (African Regional Office) in 3 countries (Kenya (May) Chad, and Mauritania). Also planning to including MOV Assessment module as part of larger revision on the Expanded Program on Immunization (EPI) Coverage Survey methodology.

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IVIR-AC	IVIR-AC should seek linkages with the WHO Alliance for Health Policy and Health Systems Research as they might be useful in priority setting and discussions.	Oct 2014	Ongoing	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 HPHSR will have a seat in the WHO Secretariat of the IVIR-AC. In addition, Initiative for Vaccine Research (IVR) will be involved in a call for proposals issued by the WHO Alliance with financial support from the Global Alliance for Vaccines and Immunizations (GAVI) and UNICEF on implementation research studies in low and middle income countries (LMICs) in 2015.
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	Subject experts on non-specific immunological effects of vaccination came together 1-2 February 2015 in Oxford to discuss and review the available evidence, identify key questions regarding non-specific effects (NSE), discuss pilot studies and its designs.
Japanese encephalitis	Interference with the immune response to other vaccinations, number of doses required and the duration of protection need to be assessed.	Apr 2006	Completed	Based on the work of the SAGE working group on Japanese encephalitis (JE), these matters were discussed at the SAGE meeting October 2014, and have been reflected in the updated JE position paper, published in February 2015
Japanese encephalitis	SAGE looked forward to better assessment of the disease burden and identification of target populations for immunization and to reviewing the regional JE control goal currently under development and the activities to achieve this goal.	Nov 2008	Completed	WHO reviewed the evidence in context of the SAGE working group on Japanese encephalitis (JE). This issue was presented in the context of the JE session at SAGE October 2014 meeting. The evidence and SAGE recommendations were included in the WHO position paper on JE published on 27 Feb 2015.
Japanese encephalitis	Guidance is needed on how to approach Japanese encephalitis (JE) vaccine impact assessments. This guidance should address surveillance data sources and analysis to measure JE vaccine impact, design of surveillance and special studies for impact measurement, JE laboratory diagnostics, and data collection and analysis for observational studies to measure vaccine effectiveness	Apr 2015	Ongoing	WHO is holding a meeting May 26-27, 2015 to be followed shortly by development of a document (analogous to the one prepared for Haemophilus influenzae type b (Hib)/pneumococcus titled "Measuring impact of Streptococcus pneumoniae and Haemophilus influenzae type b conjugate vaccination" published in 2012).

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Japanese encephalitis	Commercial kits for detection of JE-specific IgM should be compared and validated.	Apr 2006	Ongoing	Assessment using serum was carried out by PATH and published in the American Journal of Tropical Medicine and Hygiene (Am J Trop Med Hyg) July 2007. Field validation of serum and cerebrospinal fluid (CSF) in India and Bangladesh was assessed in a joint WHO/CDC (Centre for Disease Control and Prevention) meeting, at the South East Asian Regional Office (SEARO), February 2008. Nepal and Cambodia field evaluations of Japanese encephalitis (JE) assays were completed and a paper was submitted to the Journal of Infectious Diseases (JID). Assessment of kits using CSF were accepted for publication in Am J Trop Med Hyg. CDC Fort Collins distributed the 3rd serum and CSF proficiency test panel to evaluate in-house and commercial JE ELISA assays, to Western Pacific Regional Office (WPRO) JE labs in the 4th quarter of 2012. The three Western Pacific region WPR JE regional reference labs (Japan, China and Republic of Korea) held their annual coordination meeting in Chengdu, China in the 2nd quarter 2012. China Centre for Disease Control CDC JE regional reference Lab was fully accredited by WPR and HQ Lab Coordinators, in August 2012. A WPR JE LabNet meeting took place on 15 March 2013 and a Regional JE workshop for WPR was held the week of 17 June in Seoul. Submission for publication of a paper summarizing the development of the JE LabNet is pending. The Regional Reference Laboratory for JE in the WPR at the Victorian Infectious Diseases Reference Laboratory, Melbourne, was fully accredited in Oct 2013. The Global Specialized Reference Laboratory for JE at the National Institute of Infectious Diseases, Tokyo, was also fully accredited in Oct 2013. The diagnostic assay produced by PanBio ceased production at the end of 2013. An alternative assay produced by InBios with similar performance will be used in the WHO laboratory network. The training workshop at the Korean CDC in June was intended to introduce the network to this kit. A biregional laboratory training workshop and laboratory network meeting is scheduled for 17-21 August 2015, to be held at the National Institute of Health in Bangkok, bringing together JE lab staff from both WPR and SEAR South East Asian Region.

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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	Access to vaccines for Middle Income Countries (MICs) is important from a public health impact perspective as well as from an equity perspective. Also, MICs could provide a large demand volume for vaccine supply, thereby promoting competition and a healthy vaccine market to the benefit of both recipient countries and suppliers. The issue of access to vaccines for MICs is often discussed in relation to access to affordable pricing. Yet, previous work has shown that the needs of MICs span from evidence and capacity building to policy and advocacy, domestic financing, and procurement and supply. Various efforts are ongoing to support MICs, but a clear strategy and action plan in this area does not exist, nor a framework to coordinate across partners and to monitor progress. In 2012 SAGE noted with concern that these efforts are fragmented and are failing to optimize synergies in the work being undertaken by each agency. SAGE noted that with a modest investment in technical assistance and capacity building, programmes in MICs could be significantly strengthened. SAGE requested that this issue and related achievements be revisited in a subsequent meeting, and that a task force be established by WHO to coordinate the policies and efforts of partners. WHO set up a MICs Task Force in June 2014. The Task Force includes main immunization stakeholders (WHO, UNICEF, World Bank, the Global Alliance for Vaccines and Immunizations (GAVI) Secretariat, Bill and Melinda Gates Foundation (BMGF), Agence de Médecine Préventive (AMP), Sabin, Task Force for Global Health) and is working to establish a shared strategy and action plan for sustainable access to vaccines in MICs in consultation with countries, civil society organizations (CSOs), and industry. The Task Force has first focused its work on redefining the problem statement. Following these analyses it was decided that the Task Force would concentrate its efforts on non-GAVI MICs only; that the Task Force would move away from the perceived issue of a “lag” between MICs and GAVI-supported countries, and would focus instead on the fact that MICs are far from reaching their Decade of Vaccines (DoV) targets. Following the initial literature review and analytical work, the Task Force conducted country consultations to develop a need assessment that highlighted the most important needs in MICs. The Task Force also contacted 20 partners and WHO regional offices to take stock of ongoing activities to address these needs, revealing a lack of funding and focused activities outside of GAVI-countries. Following these consultations, a gap analysis was conducted, on which the Task Force built the MIC strategy. The MIC strategy is a shared and comprehensive approach with the goal to “enhance sustainable access to vaccines for populations in middle-income countries to meet Global Vaccine Action Plan (GVAP) targets”. The strategy promotes the development of a mix of new activities and existing activities that need to be expanded or modified to focus on MICs’ specific needs. In order to respect the heterogeneity of MICs and align with their national priorities, the MIC strategy was developed to be tailored to the specific needs of each MIC, around four main areas: - Strengthened decision making for timely and evidence-based immunization policy and programmatic choices; - Increased political commitment and financial sustainability of immunization programmes; - Enhanced demand for and equitable delivery of immunization services; - Improved access to affordable and timely supply. 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 investments in graduated countries. In the implementation phase, the Task Force, with WHO as Secretariat, would continue its role of coordination and information sharing.

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Malaria	SAGE requested that it be kept informed of developments in the ongoing multi-country Phase 3 trial and indicated that further discussion on the optimal schedule for a malaria vaccine will need to occur.	Oct 2009	Ongoing	The timing for the Decision session depends on the timing of the regulatory decision. The European Medicines Agency (EMA) is expected to make a regulatory decision between July and September 2015. The submission was made in July 2014. If the September 2015 timeline is met for EMA decision a SAGE/Malaria Policy Advisory Committee (MPAC) meeting joint session is expected in Oct 2015. The final results from the Phase 3 trial were reviewed by Joint Technical Expert Group (JTEG) 25-26 September 2014, and SAGE has received the JTEG meeting report. A final JTEG meeting is planned for June 29-30, at which candidate policy recommendations will be drafted for decision by SAGE and MPAC. A separate process has coordinated harmonization and comparison of the malaria models available for RTS,S/AS01 impact and cost-effectiveness predictions. The independent assessment from this process will also be presented to SAGE and MPAC. Any recommendation for use in the 5-17 month age range is likely to focus on the 5-9 month age period for the primary immunization series due to the age pattern of malaria. JTEG reviewed the data on a fourth booster dose given 18 months after the primary immunization series. If EMA gives a positive opinion, WHO recommendations for use are issued, the Global Alliance for Vaccines and Immunizations (GAVI) Board will meet to consider the updated impact estimates to make a decision on the possible opening of a window for the malaria vaccine.
Malaria	SAGE noted the utility of PPCs to developers and funders, and proposed that the opportunity for input into future PPCs at an early stage for any vaccine of public health importance could be included as part of SAGE's global public health mandate.	Apr 2013	Ongoing	Malaria Vaccine Preferred Product Characteristics were shared by email with SAGE committee members for their individual comment during July 2014. The document was published as a WHO document during January 2015 - the first of the new class of WHO Preferred Product Characteristics documents. These will provide information about WHO's preferences and processes for priority public health needs to be met by new vaccine development.
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 reviewed various regulatory approaches to labelling of the pregnancy and lactation sections of product inserts, and it has convened two meetings on the subject: a consultation at WHO in July 2014 and a session at a meeting of the Developing Country Vaccine Regulators' Network (DCVRN) in China in November 2014. No regulatory consensus was achieved in these meetings regarding data requirements for product labelling, and further consultations are planned to discuss this issue further in 2015. The meetings did identify potential alternative methods by which WHO could promote more permissive language in package inserts regarding vaccine use in pregnancy, including use of WHO Prequalification (PQ) Model Package Inserts for influenza vaccines. WHO is also exploring other mechanisms that would promote evidence-based, permissive language in package inserts and that would improve understanding of precautionary language in package inserts.

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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. SAGE recommended a 1-dose schedule, with vaccine administration by deep intramuscular injection, preferably in the anterolateral aspect of the thigh, at 9–18 months of age based on local programmatic and epidemiologic considerations. This recommendation for routine immunization programmes is based on the high level of herd immunity following mass campaigns, epidemiologic evidence on the age distribution of disease, and programmatic and economic considerations. Any children who miss vaccination at the recommended age should be vaccinated as soon as possible thereafter.	Oct 2014	Ongoing	The recommendations from SAGE are reflected in an update to the WHO meningococcal vaccine position paper. The updated guidance has been published in the Weekly Epidemiological Record WER on 20 February 2015: http://www.who.int/wer/2015/wer9008/en/. One of the meningitis belt countries (Ghana) has already submitted an application to the Global Alliance for Vaccines and Immunizations (GAVI) in January 2015 for introduction of the meningococcal A conjugate vaccine into their routine immunization programme, with a single dose at 18 months of age concomitantly with the administration of the second dose of Measles/Rubella vaccine. Other meningits belt countries intend to apply for the introducton of the vaccine into their routine programme at the next GAVI application window in September 2015.
PDVAC	SAGE requested to be updated by Product Development for Vaccines Advisory Committee (PDVAC) on the criteria used for prioritizing vaccines for IVR's work.	Oct 2014	Ongoing	SAGE will be provided with an update during the April 2015 SAGE meeting.
Pertussis	A systematic review of the optimal primary immunization schedules (in association with diphtheria, tetanus toxoid containing vaccine) is ongoing and will be presented at the October 2014 SAGE meeting. The 2010 pertussis position paper will be updated after the results of this review are available. In the meantime a short update to the position paper will be published to clarify that the previous statement on the choice of vaccine contained in the 2010 vaccine position paper no longer holds true.	Apr 2014	Ongoing	An update of the pertussis position paper was published in the Weekly Epidemiological Record (WER) on Friday July 25 2014. The systematic review was completed and a face-to-face meeting of the pertussis Working group took place at the end of August 2014. In view of the conclusions of the group that there was no evidence to recommend significant changes to the immunization schedules and in the context of the Ebola outbreak pressure, the decision was made to postpone the reporting to SAGE and related discussions to the April 2015 meeting. The publication of the full update to the pertussis position paper will then be initiated after the April 2015 SAGE meeting, and is currently planned for Q3 2015.

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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	The Global Polio Eradication Initiative (GPEI) has constituted a Legacy Working Group (LWG), currently comprised of representatives from the spearheading partners (Rotary, WHO, CDC and UNICEF) and the Bill and Melinda Gates Foundation to take forward the legacy planning work. The LWG has finalized and is implementing its workplan. One of the major activities within the workplan is to hold broad consultations with relevant stakeholders to document the lessons learnt and knowledge of the programme, to guide the direction of the legacy work, and to establish what benefit the lessons and resources of the GPEI could be to other initiatives. These consultations began in early 2014 and were continuing through the rest of the year. The consultation included plans for soliciting contributions from communities and front-line health workers' on their experiences of polio eradication. In addition, the GPEI has contracted a consultant group that will conduct in-country interviews that will include learning lessons of polio eradication. As well as having produced a paper for the Journal of Infectious Diseases (JID) on the lessons of polio eradication (Cochi, Freeman, Guirguis, Jafari, Aylward, Global Polio Eradication Initiative: Lessons Learned and Legacy), the GPEI Legacy Management Group is seeking input on lessons at the country level. This work will be led by Regional and Country-based colleagues and will involve the input of front-line workers. In addition, a team from the Boston Consulting Group supporting the legacy planning work in 2014 and early 2015 have sought input from 10 countries on contributions of polio-funded staff to other health priorities including immunization. The first segment of this work was reported to the Polio Partners Group and the Polio Oversight Board in December 2014
Polio	Sufficient capacity should be established at the global level to provide technical and programmatic support to countries to plan and implement all activities associated with type 2 oral polio vaccine (OPV2) withdrawal and introduction of inactivated polio vaccine (IPV).	Apr 2013	Ongoing	The Immunization Systems management group, co-chaired by WHO and UNICEF, has been established to coordinate efforts towards the activities relating of OPV2 (type 2 component of oral polio vaccine) withdrawal and IPV (inactivated polio vaccine)introduction. The multi partner group has been operating since mid-April 2013 in five areas of work : Regulatory, vaccine implementation, communication, financing and routine immunization strengthening. The time investment dedicated by the staff of the six agencies engaged in the Immunization Systems Management Group, IMG (Centre for Disease Control and Prevention CDC, WHO, UNICEF, Bill and Melinda Gates Foundation BMGF, Rotary and Global Alliance for Vaccines and Immunization GAVI) since April 2013 has been impressive. WHO/EPI (Expanded Programme on Immunization) has filled an additional 3 professional staff positions at HQ to contribute to this effort. UNICEF HQ has filled two additional HQ positions. Significant numbers of staff and consultants have also been deployed at Regional levels of both organizations, and funding has been sent to all regional offices. 66 out of 73 GAVI eligible countries have applied for IPV introduction support. For non GAVI countries, a financing mechanism has been rolled out to support 16 countries in Tier 2 and Tier 3 or LMIC (low and middle income countries) which are not GAVI eligible. This mechanism will enable partners to support some countries that need it with vaccine introduction grants and/or time limited procurement of IPV. As of September 26 2014, a total of 113 countries (90%) have indicated their intent to introduce IPV by the end of 2015. In December 2014 the above financing mechanism was extended to another 9 countries from the American (AM) and Western Pacific (WP) regions to help them, in a catalytic manner, initiate the procurement of IPV. The effort is now focusing on providing countries with the necessary information and technical assistance to develop a plan to carry out a switch from trivalent OPV (tOPV) to bivalent OPV (bOPV) in April 2016.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Polio	SAGE recommended working closely with countries on activities towards type 2 oral polio vaccine (OPV2) withdrawal.	Apr 2013	Ongoing	A joint letter to all oral polio vaccine (OPV)-only using countries was sent by the WHO Director General and UNICEF Executive Director, and the Global Alliance for Vaccines and Immunizations (GAVI) CEO where applicable, highlighting the importance of inactivated polio vaccine(IPV) introduction and outlining the SAGE recommendation on IPV introduction schedules and planning timelines. All regions have held, or will have held by the end of this year, at least one meeting that included a substantive focus on IPV introduction. In addition, many regions have held GAVI application development workshops; this has led to all 72 eligible countries applying for support already. Joint WHO/UNICEF regional coordination mechanisms are established to ensure countries are suitably supported in the decision making process and in the development and implementation of introduction plans. A large number of countries (120 of 126) have confirmed decision or intent to introduce IPV by end of 2015 in preparation for the withdrawal of type 2 OPV. Work is now ongoing to i) ensure that declared intent materializes into commitement and ii) countries with no plan developed for IPV introduction have one ready before the end of the year. The matter of OPV withdrawal was discussed by the WHO Executive Board at it January 2015 session. The Board endorsed a secretariat recommendation that a WHA resolution be drafted and put forward in May 2015 on this subject. In the interim high level communication will be initiated with all 156 OPV using countries to encourage them to develop a plan of action for the withdrawal of OPV and replacement with bOPV which should be ready by september 2015. Technical materials and standard operating procedures (SOPs) have started to be shared with countries through regional consultations.
Polio eradication	SAGE requested that the Polio working group draft the necessary protocols for the 5 major components of the proposed strategy for type 2 virus detection and response after OPV2 cessation, in the areas of virus notification, surveillance, vaccine stockpiles, response and management of travellers for presentation to the SAGE in 2014.	Nov 2013	Completed	SAGE reviewed the presented protocols for the 5 major components of the proposed strategy in October 2014, and endorsed them.
Polio eradication	"To facilitate prioritization, planning and implementation of IPV introduction at country level, SAGE recommended that consideration be given to developing a resolution on accelerated IPV introduction for submission to the World Health Assembly (WHA) in 2014."	Nov 2013	Ongoing	The World Health Assembly (WHA) noted the progress of inactivated polio vaccine (IPV) introductions in 2014, based on the report from Immunization systems Management Group (IMG). During the WHA 2014, the 5 criteria for withdrawel were discussed. These criteria include a) status of introduction of IPV in oral polio vaccine OPV-only using countries, b) registered bivalent OPV for routine immunization, c) establishment of stockpile and outbreak response protocol for type 2 virus, d) completion of phase 1 containment activities under the Global Action Plan (GAP) and e) affirmation of wild poliovirus type 2 eradication by the Global Commission for the Certification of the Eradication of Poliomyelitis (GCC). In 2015 a session at the WHA is held to endorse the envisioned timing of the switch (currently scheduled in April 2016).
Reports from other advisory committees	SAGE recommended appointment of appropriate programmatic and implementation expertise to IVIR-AC membership including representation of experts from low and middle-income countries.	Nov 2011	Ongoing	Since 2013 Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) includes two programmatic and implementation research members from the African Region (AFR) and the South East Asian Region (SEAR). Since 2014 IVIR-AC includes a mathematical modeler/economist from SEAR and a medical anthropologist from AFR. Currently 2 seats are vacant for a mathematical modelers and one health economists with experience in vaccine implementation research. Recruitment of new members is ongoing.
Reports from other advisory committees on immunization	WHO and NIBSC should develop with other stakeholders, a business plan to assure long-term security of the development of WHO reference preparations as a global public health resource and additional efforts should be undertaken to disseminate outcomes of the committees deliberations and to explain the relevance of its work to the broader immunization community.	Nov 2006	Pending	A comprehensive review of the work of the Expert Committee on Biological Standardization (ECBS) is still pending. The review will include (but not be restricted to) consideration of communication of ECBS outcomes.This will be linked with an overriding review of Expert Committees by the department of Essential Medicines and Health Products. Discussion on a paper on the process of the review was initiated by ECBS during its October 2014 meeting; however biotherapeutic biological drugs were identified as first priority.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Security of vaccine supply	SAGE requested WHO to produce a report on the security of the supply of affordable vaccines and encouraged donors to invest in the development of new vaccine technologies that facilitate the delivery of effective, affordable vaccines to populations most at risk.	Apr 2012	Ongoing	Discussion with donors has advanced well and planning for meeting on new vaccine technologies being initiated. Internal WHO discussions are in progress. A meeting on new vaccine technologies was held in February 2014. The work on the supply of affordable vaccine is an on-going effort in which all immunization partners are engaged. Affordability of vaccine remains an ongoing challenge for a number of countries however recent accomplishments in the area of inactivated polio vaccine (IPV) supply and financing are a good indication that the trend is evolving positively through strong partnership between the public and the private sectors. Given the amount of work going on in this area under several other initiatives including those reflected under item "Lower middle-income countries: Sustainable adoption and financing for new vaccines", we have discussed internally and have decided that, for the time being the production of a report was not warranted. SAGE will be kept informed on an ongoing basis of progress made and new developments. More information on the topic of financing can be found at under the respective topic in the tracking sheet. No further development to report at this stage
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	An operational framework for vaccine donation has been developed adn agreed by the Global Health Security Intitiative (GHSI) Medical countermeasures (MCM) task force.WHO and Japan agreed on the donation of 10.000 doses of LC16m8 vaccine from Kaketsuken.WHO is working with the manufacturer to ship the vaccine to Geneva. The agreement with France for the donation of 5 million doses of vaccine still ongoing, depending on the prequalification (PQ). WHO is working on smallpox vaccine prequalification for WHO stockpile.
Supply Chain	SAGE requested future update on approaches to prioritization within supply chain improvement plans.	Oct 2014	Ongoing	Under the umbrella of the WHO-UNICEF Immunization Supply Chain and Logistics Hub, a process has started to implement the more holistic approach to immunization supply chain improvement planning as part of the WHO-UNICEF Joint Statement that was endorsed by the SAGE. The approach builds in a methodology to prioritize strategies and activities that will have the largest impact on immunization supply chain improvements. In addition, evidence around cost-effective solutions is being compiled by the Hub which will be transformed into an Solutions Toolbox to help countries tailor and prioritize the right solutions. 5 countries have developed a supply chain improvement plan - Pakistan, Democratic Republic of Congo, Lao People's Democratic Republic, Bangladesh, and Nepal.

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	During 2013, a global strategic review was conducted of the invasive bacterial vaccine preventable diseases (IB-VPD) and rotavirus sentinel hospital surveillance networks. During that meeting, 50 recommendations were made to advance the status of both networks. During 2014, significant progress was made to further improve the IB-VPD and rotavirus sentinel hospital surveillance networks. Network management was strengthened with the use of a Performance Management Framework to track implementation status of annual global recommendations. A major achievement was the transition to standardized, case-based reporting with quarterly data sharing plus feedback of standard process and performance indicators to sites. Data management processes continue to be improved toward having 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 (EQA) program as well as quality control (QC) programmes. Sentinel site and laboratory assessments have been prioritized but have not been able to include all priority sites. The most recent 2013 data available for the meeting may underestimate data quality because none of the actions taken after the 2013 strategic review are yet reflected. IB-VPD data analysis focused on assessing laboratory testing performance of culture and PCR, and found <30% of PCR results were linked into the clinical database as well as a 3-fold improved detection of pathogen by PCR over culture alone. Beginning in 2014, Regional Reference Laboratories (RRLs) will only process specimens with a unique identification number and it is thus anticipated that a larger percentage of cases will have clinical data that can be linked with RRL data. Network data has contributed to vaccine introduction decisions and the surveillance networks have been used as platforms for vaccine impact evaluations. Moving forward, the rapid introduction of Pneumococcal Conjugate Vaccine (PCV) and Rotavirus Vaccines (RV) by Member States now requires the surveillance networks to focus on improving baseline data for sites in non-vaccine using Member States and to ensure consistent surveillance practices for sites that meet inclusion criteria in vaccine-using Member States. The web-based data management tool has great potential to improve data quality and may be expanded to other vaccine preventable diseases in due course. WHO, the iTAG (informal Technical Advisory Group) and partners will work to implement recommendations to further improve the network during 2015 including to strengthen programme management: • Strengthen involvement of Ministry of Health and national EPI (Expanded Programme on Immunization) programmes; • By end-April 2015, IB-VPD specimen sharing agreements should be established between all 71 IB-VPD target hospitals and RRLs to further increase access to PCR's improved diagnostic yield; • All IB-VPD cerebrospinal fluid specimens should be tested by PCR at an RRL; • Further focus efforts and define a subset of sites where PCV and/or RV vaccine impact evaluations may be feasible due to sufficient pre- and post-vaccine introduction data; And to Improve data management and analysis: • Link clinical and laboratory data by use of unique identification numbers. Prospective data linking established by 31 Dec 2014, and sites prioritized for retrospective linking; Validation of thesea activities pending until June 2015. • Zero reporting to be implemented at all sites by 31 Dec 2014; In March 2015, regional activities are in progress, but zero reporting not yet been implemented. • Identify a subset of core data variables for vaccine impact assessments; • Draft guidelines for rotavirus data analysis/interpretation and assess probable bacterial meningitis data; • Finalize the web-based data management tool; • Revise site inclusion criteria: for rotavirus, reduce the number of annual stool specimens tested in vaccine using countries; for IB-VPD, include consistently performing sites that enrol fewer meningitis cases.

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	In December 2012, the first consultation of the TB Technical Expert Group (TEG) was held to review clinical trial plans for two advanced new TB vaccine candidates, VPM1002 (VPM, Germany) and M72 (GSK Biom, Belgium). Written update to SAGE was provided ahead of the November 2013 SAGE meeting. The 2014 annual update on TB vaccines was provided in Oct. 2014.
Typhoid	Establish a SAGE working group on typhoid conjugate vaccines in 2016 to prepare for a SAGE review of the evidence in 2017.	Oct 2014	Pending	The plan is to establish the Working Group in 2016 to prepare for a SAGE review in 2017.
Un/under-immunized children	SAGE requested that WHO quickly roll out tools so that other countries can address low coverage of vaccination.	Nov 2010	Ongoing	The in-depth tool "A Guide to Tailoring Immunization Programmes (TIP) has already been developed and used by WHO-EURO (European Regional office). Currently the Univ. of Witwatersrand in South Africa has been contracted to adapt the methodology to developing countries, and less intensive consultant-based inputs.
Vaccination in 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	The Emergency Risk Management and Humanitarian Response (ERM) Department was slow in the uptake of this recommendation due to lack of staff and the high number of Level 3 emergencies.
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	To improve the precision and usefulness of survey results and to reduce the cost of surveys, the Strategic Information Group (SIG) proposes to explore 1) recent advances in sampling methodology, 2) new technologies for constructing sampling frames, supervision of field work, data collection, and analysis and 3) alternative content, collection, analysis, presentation and linkages with other data sources. An explicit description of precision, usefulness and cost of various trade-offs between alternative methods will constitute part of the exploration. An initial meeting was convened of the Department of Immunization Vaccines and Biologicals' (IVB) Informal Advisor Group on Monitoring Immunization Programme Performance through Household and Community Surveys. First meeting addressed the need to modify Demographic and Health Surveys (DHS) - implemented by ICF International; the UNICEF Multiple Indicator Cluster Surveys and the WHO Immunization Cluster Survey to accommodate changes in immunization system strategies. On 17-18 September 2012 a meeting was held with representatives of ICF and UNICEF to discuss modifications to their standard recommendations on data collection, analysis and presentation of immunization coverage data. WHO and UNICEF provided written recommendation to these agencies. An informal working group has been created to review and revise WHO guidance on measuring immunization coverage through household and community surveys. The working group met in July 2013 to agree on the scope of work, to identify initial products, and establish a plan of document production, review, pilot testing, and clearance. Draft guideline was circulated to external reviews. Protocol for pilot testing was developed and pilot testing is currently undergoing in Bangladesh. The methods will be reviewed in September by Immunization and Vaccines Related Implementation Research (IVIR) Advisory Committee. The proposed methods were reviewed in September by Immunization and Vaccines Related Implementation Research (IVIR) Advisory Committee. The methodology is currently tested in Burkina Faso and in Lao PDR and manual will be updated based on the inputs.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Vaccine coverage	WHO to identify appropriate methods and develop guidelines for collecting, analysing, and interpreting biomarkers for validating coverage.	Nov 2011	Ongoing	WHO to identify appropriate methods and develop guidelines for collecting, analysing, and interpreting biomarkers for validating coverage. A draft document which reviews, for a selected list of vaccine-preventable diseases, laboratory test available and associated requirements for specimen collection/transport, personal experience and training, and laboratory supplies and equipment has been prepared. The draft will be reviewed internally and following recommended changes will be submitted for review by external experts. For each selected disease study populations, sampling methods, data/specimen collection, laboratory/statistical analysis, and implications of results were summarized in an accompanying document. Work in progress was presented to WHO and UNICEF Regional Focal Points for immunization during the Meeting on Monitoring National Immunization Systems, 9-11 October 2012 for their comments. Internal and external review of the document will continue and after incorporating the comments draft guidelines will be developed for use of sero-surveillance as an evaluation tool for immunization programmes. 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 subtasks in developing parts of these guidelines that pertain to their respective expertise. A working draft will be finished by the end of Q4/2014 and will be tested subsequently in pilot studies in two different settings, pre- and post-campaign, for its applicability. These pilot studies are expected to take start Q1 2015 and will run during the entire year of 2015. Based on the outcome, the working draft guidelines will be corrected where needed and finalised. The final document is planned to be ready by Q1 2016 and to be rolled out as a tool to evaluate the immune status of the target or targeted population.A draft has been circulated for comments and will be tested subsequently in pilot studies in two different settings, pre- and post-campaign, for its applicability. These pilot studies are expected to take start Q1 2015 and will run during the entire year of 2015. Based on the outcome, the working draft guidelines will be corrected where needed and finalised. The final document is planned to be ready by Q2 2016 and to be rolled out as a tool to evaluate the immune status of the target or targeted population.
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	As the Bill & Melinda Gates Foundation is now accepting Letters of Inquiry for the development of an easy-to-use tool that rapidly assesses the immune status of children against select vaccine-preventable diseases. Inquiries will be welcome that focus on prototype development and detail plans for future commercialization possibilities.
Vaccine Hesitancy	SAGE acknowledged the necessity to develop core capacities at headquarters and regional level for gaining behavioural insights that can be applied in an integrated fashion for prevention of many communicable and non-communicable diseases, as well as vaccine hesitancy. This will require the involvement of sociologists, psychologists, anthropologists, experts in social marketing, communication experts, and specific disease and vaccine experts.	Oct 2014	Ongoing	Discussions are ongoing within WHO and UNICEF and with partners on how to collectively establish core capacities in order to support and provide technical assistance to countries. For this, discussions were intiated on how to advance the establishment of a network of expertise/excellence and collaborating centres by capitalizing on currently ongoing initatives and activities which have been established and are conducted by WHO (HQ and Regions), partners and stakeholders in the field of vaccine hesitancy.
Vaccine Hesitancy	SAGE encourages validation of the developed compendium of survey questions on vaccine hesitancy, which have been assessed and validated only in some high-income countries or not at all.	Oct 2014	Ongoing	Discussions with various stakeholders are ongoing (Centre for Disease Control CDC, WHO, European Regional Office EURO, Middle Income Countries MIC task force) on the ways forward to identify partners to take on the validation of the survey quesions.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Vaccine Hesitancy	SAGE underlined the importance of distributing the matrix of determinants, the definition of hesitancy and the other deliverables to countries and partners.	Oct 2014	Ongoing	Discussions and presentations were held in teh context of the immunization managers' meeting in the Eastern Mediterranean Region (EMR) and the African Region (AFR) Task force on immunization(TFI) meetings. A series of 9 full paper plus one editorial has been submitted to the journal Vaccine and will be published as a supplement. The online version should be accessible early April at the latest.
Vaccine safety	SAGE highlighted the urgent need for a safety review of other important vaccines that could be used during pregnancy.	Nov 2012	Ongoing	A sub-group of the Global Advisory Committee on Vaccine Safety (GACVS) has been launched to address vaccine safety during pregnancy. A finalized version of the GACVS report on safety of immunization during pregnacy has been made available to SAGE in November 2013 and is now available on the Global Vaccine Safety (GVS) website. A new work track was started with WHO Initiative for Vaccine Research (IVR) in order to harmonize safety monitoring during pregnancy clinical trials. WHO is a contributor to the Gates funded Global alignment of immunization safety assessment in pregnancy project that should run until the end of 2016.
Vaccine Supply	It was noted that SAGE needs to address the constraint experienced across Regions of repetitive shortfalls in vaccine supply, both for existing vaccination programmes (in particular for DTP-containing vaccines) as well as for new/emerging vaccines, and the impact on vaccine coverage in several countries.	Nov 2012	Ongoing	Concerns about the ongoing shortages of traditional vaccines persist. Recent discussions with UNICEF SD (Supply Division) have indicated that a vaccine such as BCG may face supply shortages in 2015 to the extent of being unable to deliver vaccines to all countries needs, potentially prompting stock-outs. For other vaccines, including measles containing vaccines, supply is currently adequate, but largely dependent on a single manufacturer.
Yellow Fever	SAGE requested WHO to revisit the IHR provisions relating to the period of validity for international certificates for vaccination against yellow fever (YF).	Apr 2013	Ongoing	The WHO World Health Assembly in May 2014 adopted an amendment to Annex 7 of the International Health Regulations (2005) (IHR), which stipulates that the period of protection afforded by yellow fever vaccination, and the term of validity of the certificate will change from 10 years to the duration of the life of the person vaccinated. This change will enter into force legally in June 2016. Until then the current IHR text on yellow fever vaccination and certificates continues to apply, and some countries may continue to request proof of vaccination or a booster within the last 10 years from travellers. As of the end February 2015, 22 countries have notifed WHO that already accept the validity yellow fever (YF) vaccination certificate for life. Starting with the online 2015 International Travel and Health (ITH) edition, WHO will report on the status of YF vaccination requirements for countries.

World Health Organization

EXECUTIVE BOARD
136th session
Provisional agenda item 5.1

EB136/INF./2
12 December 2014

Framework of engagement with non-State actors

Information on regional committee debates

1. As requested by the World Health Assembly in decision WHA67(14), the Director-General prepared a comprehensive report of the comments made by Member States during the Sixty-seventh World Health Assembly and the follow-up comments and questions raised, including clarification and response thereon from the Secretariat, and submitted it for the consideration of the six regional committees. This report summarizes the feedback received from the regional committees.[1]

2. The **African Region** considered the issue at the meetings of its Programme Subcommittee held in advance of the Regional Committee session. In the discussions of the **Regional Committee**, the following key issues emerged: interaction with non-State actors is essential; the transparency of the processes is an imperative; however, there is a lack of clarity in the process and criteria regarding due diligence and related procedures. WHO should develop a comprehensive policy on conflicts of interest in the framework of engagement with non-State actors. It was emphasized that WHO should proceed with caution in developing a policy on engagement with non-State actors, as such a policy would have far-reaching implications for the Organization.

3. Other issues raised included reservations regarding the earmarking of funds from private sector non-State actors, as well as the use of such funds for the payment of staff salaries; concerns regarding the influence of non-State actors on WHO's normative and standard-setting work; and strong reservations regarding staff secondments to WHO from the private sector.

4. Furthermore, although there was agreement that WHO should not engage with the tobacco and arms industries, a number of Member States considered that this restriction should be extended to other sectors, including notably the alcohol, food and beverage industries. It was underscored that decision-making within WHO governing bodies should remain the exclusive prerogative of Member States.

5. Representatives requested more time to allow for consultation at the national level. It was noted that Member States could raise concerns at the Executive Board session in January 2015, including through the Executive Board members from the African Region.

[1] Additional information requested by Member States is available on the following website: http://www.who.int/about/who_reform/non-state-actors/en/.

6. The following recommendations were made:

(a) representatives should further consult on this matter at country level and share the outcome of these deliberations with Executive Board members from the African Region and with the Regional Office Secretariat, with a view to developing a regional position in time for the Sixty-eighth World Health Assembly in May 2015;

(b) the revised framework should provide a clear policy on how WHO will manage conflicts of interest and define its due diligence processes;

(c) the revised framework should better reflect the role and function of academic institutions, in particular regarding how such institutions can complement WHO's work.

7. The **Regional Committee for the Americas** recognized the importance of collaboration with nongovernmental organizations, academic institutions and other non-State actors in order to have access to appropriate expertise and resources and advance public health mandates, but stressed that real or perceived conflicts of interest must be avoided. Identification of the potential risks and formulation of specific principles and guidelines for engagement with the various categories of non-State actors were seen as essential. It was considered that the framework set out in World Health Assembly document A67/6 lacked detail regarding the criteria that non-State actors must meet in order to be classified in each category and the way in which each group could engage with WHO. At the same time, Member States cautioned against the adoption of an overly prescriptive framework that might not allow sufficient flexibility. It was recommended that an early review should be undertaken after the framework is adopted in order to identify any needed adjustments.

8. Several Member States were of the view that any interaction with actors whose activities or products were harmful to health and any secondment of personnel from the private sector should be expressly prohibited. The need to determine whether nongovernmental organizations and philanthropic and academic institutions received funding from for-profit private companies was highlighted. Member State involvement in monitoring and oversight of relations with non-State actors was considered essential. Some Member States questioned, however, whether a committee of six members under the Executive Board, as proposed in document A67/6, would ensure adequate governmental representation and participation.

9. It was pointed out that PAHO has had considerable experience in interacting with non-State actors, including with the pharmaceutical industry through the Organization's Revolving Fund for Vaccine Procurement, and the Pan American Sanitary Bureau was encouraged to share that experience with the WHO Secretariat.

10. The **Regional Committee for South-East Asia** acknowledged the major and growing role of non-State actors in all aspects of global health, reiterating that the overall objective of WHO's engagement with such actors is to work towards the fulfilment of the Organization's mandate by making better use of resources. The recommendations of the Inter-sessional Meeting[1] to the Committee were considered, including the changes proposed by Member States of the Region to the draft framework of engagement and associated policies/operational procedures drawn up by WHO. The chief concern of the Committee was that, in its engagement with non-State actors, the integrity

[1] Document SEA/RC67/3 Add.1 (http://www.searo.who.int/mediacentre/events/governance/rc/rc67-3add1_agenda_6.1.pdf?ua=1).

and neutrality of WHO should not be compromised. The Committee noted that there were no secondments to WHO from the private sector; most were from specialized agencies of the United Nations system, which did not fall under the category of non-State actors, being sister agencies. The Committee requested that the report and recommendations of the Inter-sessional Meeting held in August 2014 should be taken into consideration when revising the draft framework of engagement with non-State actors so that no secondments from non-State actors take place in WHO.

11. The **Regional Committee for Europe** adopted the following statement on the position of the Member States in the European Region with regard to the draft framework of engagement with non-State actors:

> "The WHO and its good name are precious to us, and we, the Member States of the European Region, will work diligently and attentively with the Secretariat to ensure it remains relevant and effective in the 21st century. To this end, recalling our readiness to adopt it at the Sixty-seventh World Health Assembly, we strongly urge adoption of the Framework of engagement with non-State actors at the Sixty-eighth World Health Assembly in 2015.
>
> We acknowledge that some further improvements could be made, with the aim of increasing clarity, including in the following areas:
>
> – the management of conflicts of interest;
> – the process and time table for evaluation.
>
> We advise strongly against trying to perfect every detail, preferring instead to begin work, trusting in the wisdom of the governing bodies to oversee the operation of the framework in practice and continue to improve it. We look forward to receiving the updated framework by 15 December, and would request the Secretariat to address it at the planned mission briefing in mid-December 2014 with web access for Member States."

12. The **Regional Committee for the Eastern Mediterranean** deliberated the framework of engagement with non-State actors as part of WHO reform. The Regional Committee supported the need for comprehensive guidelines for WHO interaction with non-State actors. It noted the commitment of Member States of the Region to contribute to improvement of the framework, including its monitoring and evaluation components. The areas for improvement should include the management of conflicts of interest, clarification of boundaries, especially with the private sector and business associates, definition of actors, acceptance of donation of pharmaceutical products and technology transfers.

13. At the **Regional Committee for the Western Pacific**, representatives endorsed the framework of engagement with non-State actors as a tool for giving WHO the flexibility to work with global health actors from all sectors, while protecting its integrity as the global standard-setting Organization for health. For example, subject to appropriate safeguards, WHO should be able to engage with the private sector in its commercial capacity to advance the research and development of new medical products.

14. It was also noted that WHO was constitutionally mandated to work with other sectors in areas such as nutrition, housing, sanitation, recreation and environmental hygiene, as well as the development of standards on food, biologicals and pharmaceutical products. The concept of competitive neutrality should be embedded in the framework. The combination of an evaluation process to ensure continuous improvement, robust and regular oversight by the World Health

Assembly through the Executive Board, and a mechanism to discontinue engagement with particular non-State actors, if required, should be sufficient guarantees to ensure the adoption of the framework by the World Health Assembly.

15. Another representative observed that, at the recent regional meeting of the Pan American Health Organization, it had been suggested that a dedicated office could be established to oversee implementation of the engagement policy. Such an office could not only exercise a watchdog function but also play a facilitating role in promoting engagement and actively support WHO programmes in their efforts to reach out to non-State actors, including the private sector. Mechanisms for receiving funds from private sector entities should be aligned with national health sector strategies.

16. There were opportunities for WHO to learn from successful multistakeholder initiatives and public–private partnerships, which could subsequently be shared with Member States.

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Ebola: ending the current outbreak, strengthening global preparedness and ensuring WHO's capacity to prepare for and respond to future large-scale outbreaks and emergencies with health consequences

The Executive Board,

Having considered the reports on WHO's response to the Ebola virus disease outbreak;[1]

Deeply concerned by the 21 831 cases and 8690 deaths reported to date and the continuing infections and deaths in affected countries, as well as the potential risk of spread to neighbouring countries and beyond;

Emphasizing the need for Member States[2] and other relevant actors to extend urgently all possible means of support to the affected and highly at-risk countries to end the Ebola outbreak, and stressing the importance of evidence-based responses and community engagement to prevent fear, stigma and discrimination;

Reaffirming that the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being, and reiterating its determination to take further action on social determinants of health;

Recognizing that the current outbreak demonstrates once again the urgency for all countries of having strong, resilient and integrated health systems capable of fully implementing the International Health Regulations (2005), and of having the capacity for health-related emergency preparedness and progress towards universal health coverage that promotes universal, equitable access to health services and ensures affordable, good-quality service delivery;

Recalling resolution WHA64.10 on strengthening national health emergency and disaster management capacities and the resilience of health systems, which reaffirms, inter alia, that countries should ensure the protection of health, safety and welfare of their people and should ensure the resilience and self-reliance of the health system, which is critical for minimizing health hazards and vulnerabilities;

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[1] Documents EBSS/3/2, EBSS/3/3, EBSS/3/INF./1–5.

[2] And, where applicable, regional economic integration organizations.

Committed to an effective and coordinated response both for the current Ebola crisis and to make the corrective changes needed to prevent, detect and contain future outbreaks, and reaffirming the central and specialized role played by WHO in emergency preparedness and response, including in health emergency situations as described in Health Assembly resolutions WHA54.14, WHA58.1, WHA59.22, WHA64.10, WHA65.20 and WHA65.23;

Recalling resolution WHA65.20, which affirms WHO's role as the health cluster lead in responding to the growing demands of health in humanitarian emergencies, and recognizes the specific requirements for effective health-related emergency operations;

Recalling that the WHO's Emergency Response Framework has so far been the basis for WHO's role, responsibilities and work in all emergencies with public health consequences;

Reaffirming WHO's responsibilities under the International Health Regulations (2005);

Noting that an effective response during an outbreak requires all levels of the Organization to continually adapt and adjust resource allocation, methods of work and information practices, with a clear focus on results;

Emphasizing in this respect that the response at all levels of WHO must be guided by an all-hazards health emergency approach, emphasizing adaptability, flexibility and accountability; principles of neutrality, humanity, impartiality, and independence; and predictability, timeliness, and country ownership; and building on effective collaboration within the Organization's mandate with other relevant actors;

Reaffirming the global strategy and plan of action on public health, innovation and intellectual property;

Acknowledging that there is a linkage between addressing Ebola, including the control and elimination of neglected tropical diseases, and the global strategy and plan of action on public health, innovation and intellectual property and a pooled fund of global health research and development;[1]

Commending all Member States,[2] organizations, including nongovernmental organizations, other entities and individuals that have provided assistance in cash and in kind, including the large number of medical professionals in response to the Ebola outbreak;

Recognizing the urgent need for an improved and more effective and coordinated response capacity for the international community, and especially for WHO and Member States,[2] in responding to health-related emergencies;

Committing to further mobilize resources to strengthen national, regional and global preparedness and preventive tasks against the threat posed by infectious diseases to global health and strong, sustainable and balanced growth for all;

[1] See resolution WHA66.22.

[2] And, where applicable, regional economic integration organizations.

Emphasizing also the fundamentally civilian character of humanitarian assistance, and reaffirming, in situations in which military capacity and assets are used as a last resort to support the implementation of humanitarian assistance, the need for the use to be undertaken with the consent of affected States and in conformity with relevant provisions of international law,[1]

Current context and challenges; stopping the epidemic; and global preparedness

1. EXPRESSES its unwavering commitment to contain the Ebola outbreak and to remain engaged in promoting urgent actions to accelerate prevention, detection, control and treatment until we reach zero cases of Ebola virus disease; to contribute to building resilient health systems in the affected countries and other highly at-risk countries; and to provide support for people who have survived Ebola, and their families, and for children orphaned by the disease, including psychosocial support;

Leadership and coordination

2. RECALLS and REAFFIRMS the constitutional mandate given to WHO to act, inter alia, as the directing and coordinating authority on international health work, and to furnish, in emergencies,[2] necessary aid upon the request or acceptance of governments, and recognizes the need to accelerate ongoing reform of the Organization;

3. FURTHER REAFFIRMS WHO's role as the lead agency of the global health cluster, including its role to ensure the timely declaration of appropriate response levels to humanitarian emergencies with health consequences, and calls on Member States[3] and relevant actors in humanitarian situations with health consequences to support WHO in fulfilling its role as lead agency of the Global Health Cluster within its mandate;

4. FURTHER REAFFIRMS that, in connection with the declaration on 8 August 2014, by the WHO Director-General that the 2014 outbreak of Ebola virus disease in some West African countries is a public health emergency of international concern, all WHO authorities with respect to the administration, deployment and other human resource matters concerning preparedness, surveillance and response rest with the Director-General, and shall be exercised in a manner consistent with the principles and objectives of WHO's Emergency Response Framework, while minimizing the negative impact on regular and routine work of WHO;

5. INVITES the Director-General to consider assigning, immediately following the Special Session, for the duration of the outbreak of Ebola virus disease, a Special Representative with the appropriate grade and authority to be responsible for all aspects of coordination at all three levels of the Organization and response for the current outbreak;

6. REAFFIRMS the authority of the Director-General to reallocate existing resources, as appropriate and needed, subject to existing authorities, procedures and agreements, without compromising the Organization's programme priorities, as needed to enable an efficient and accelerated response to end the current epidemic of Ebola virus disease;

[1] See United Nations General Assembly resolutions 60/124 and 69/135.

[2] See also resolutions WHA34.26, WHA46.6, WHA48.2, WHA58.1, WHA59.22, WHA64.10 and WHA65.20.

[3] And, where applicable, regional economic integration organizations.

7. AFFIRMS the essential role of the WHO country representatives in any outbreak and response situation and expects all levels of the Organization to cooperate with and support the Director-General in her duty to take all necessary measures so that each country office, in particular for affected and highly at-risk countries and areas, has the right skill set and expertise to match the public health challenges they face;

8 FURTHER AFFIRMS the critical role of the WHO regional offices in any outbreak and response situation, under the authority of the Director-General, and requests the Director-General and Regional Directors to take all measures for the highest level of coordination and collaboration among all levels of the Organization to jointly meet the public health challenges they face, including measures to strengthen the routine and immediate sharing of information on outbreaks of infectious diseases or emergencies with health consequences;

9. REQUESTS the Director-General to further improve communication, coordination, and information sharing between WHO and the United Nations Mission for Ebola Emergency Response, to enable Member States[1] and other partners to engage more effectively in the response, and requests a report outlining the specific role of WHO within the United Nations Mission for Ebola Emergency Response by March 2015;

10. CALLS ON the Director-General to improve the transparency and reliability of health-related needs-assessment processes;[2]

Health systems

11. CALLS ON Member States[1] to further strengthen coordination on personnel, logistics, supplies, equipment and related infrastructure, with a view to accelerating the effective response to Ebola virus disease and converting it to longer-term health system strengthening, particularly in the most affected countries, building on the results of the WHO meeting held in Geneva on 10 and 11 December 2014 on "Building resilient health systems in Ebola-affected countries" and the implementation of the International Health Regulations (2005), and in this context requests the Director-General to give technical advice to the most affected countries for developing their country plans, to be discussed in an upcoming conference;

12. ENCOURAGES Member States[1] to consider promoting health system strengthening and core capacities required under the International Health Regulations (2005) for inclusion in the implementation of the health goal of the post-2015 development agenda;

13. CALLS ON Member States[1] to strengthen capacities to recruit, develop, train, and retain the health workforce in developing countries, particularly in the most affected and highly at-risk countries;

14. FURTHER CALLS ON Member States[1] to strengthen support for health care workers to enable local and regional surge capacity, as the most important basis for emergency and outbreak response, which includes ensuring the availability of adequate isolation, care and treatment facilities and essential supplies, and strengthening national and regional capacities for surveillance, including providing support for developing countries to build capacity;

[1] And, where applicable, regional economic integration organizations.

[2] See United Nations General Assembly resolution 60/124.

15. URGES Member States[1] to establish, promote and foster regional and subregional collaboration, as well as interregional cooperation within WHO, including sharing of experience and expertise for capacity development to strengthen the role of the local health systems and workforce in the response to emergencies and other crises;[2]

16. REAFFIRMS that integrated health care, based on access to health and universal health coverage, is the best approach for strengthening health systems, and calls on Member States[1] to accelerate implementation efforts;[3]

17. TAKES NOTE of the current challenges facing the operational response to the outbreak of Ebola virus disease, as described in document EB136/26, endorses the steps outlined to meet these challenges, as described in document EBSS3/INF./5, and requests the Director-General to ensure that the required human and other resources are deployed to this end as a matter of priority and urgency;

Medical assistance

18. RECOGNIZES the importance of providing for, as much as possible, the safety and protection of health care workers, taking into account the resolution on global health and foreign policy adopted by the United Nations General Assembly on December 5, 2014;[4]

19. CALLS ON health service providers to ensure that health workers are provided with adequate training and protective gear necessary to minimize their risk of infection from disease;

20. CALLS ON Member States[1] affected by outbreaks and health emergencies to provide adequate security to protect all health workers from violence;

21. REAFFIRMS the value of foreign medical teams to the outbreak response, and requests the Director-General to ensure WHO is able, building on the newly established Foreign Medical Teams unit at WHO, to coordinate offers of and requests for the deployment of equipped and experienced foreign medical teams to fill urgent needs and to systematize the formation, training, and support for these foreign medical teams in a timely manner;

22. FURTHER REAFFIRMS the value of ensuring the effective deployment of all possible health services, reserve medical teams and the vital consumables to control diseases, by a process of consultation, coordination and integration based on the request or acceptance of the host countries, recognizing that foreign medical teams are intended to support temporarily the national health system, with a view to its sustainable strengthening;

23. REQUESTS the Director-General, in consultation with Member States,[1] to further develop mechanisms for the use of existing emergency stand-by capacities, including, where appropriate, regional humanitarian capacities, through formal agreements, and to report on the issue to the Sixty-ninth World Health Assembly;[5]

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[1] And, where applicable, regional economic integration organizations.

[2] See resolution WHA64.10.

[3] See resolutions WHA67.24 and WHA63.16.

[4] Resolution 69/132.

[5] See United Nations General Assembly resolution 60/124, paragraph 13.

Information

24. CALLS ON Member States,[1] consistent with the International Health Regulations (2005), to strengthen disease surveillance capacity and data and information flows between local and national levels and with WHO at country, regional and global levels in order to enable a full and effective response to the current epidemic of Ebola virus disease, and to ensure early reporting and detection for any future outbreak;

25. REQUESTS the Director-General to take all necessary steps to strengthen surveillance, effective and timely dissemination of data and information, and health information capability, required to control the epidemic, and to apply lessons learnt to future WHO work in this regard;

26. FURTHER REQUESTS the Director-General to develop, integrate, and support common tools and coordination mechanisms, such as web portals, as appropriate, to track activities across all aspects of WHO's work to end the current outbreak of Ebola virus disease, and identify gaps and formulate concrete needs in order to prevent and respond more effectively to future outbreaks;

27. FURTHER REQUESTS the Director-General to ensure, in the context of the present emergency, that relevant information, especially concerning details of assistance pledged and delivered to the response effort is shared actively, and in a timely and transparent manner, with Member States[1] and other partners, with a view to facilitating effective resource use and response, and requests relevant Member States[1] to assist the Director-General by providing all such information to the United Nations Office for the Coordination of Humanitarian Affairs through their financial tracking service in a timely and transparent manner;

Preparedness

28. RECOGNIZES the urgency, in the context of the current outbreak, of addressing the immediate needs in preparedness and response capacity, in particular in highly at-risk states, as identified by WHO, and calls on all Member States[1] and the international community to enhance this effort, giving appropriate priority to the disease surveillance, preparedness, and emergency work of WHO;

29. FURTHER RECOGNIZES the importance of addressing longer-term systemic gaps in capacity to prevent, detect, protect against, control, and provide a public health response to, the international spread of disease and calls on Member States[1] to fulfil their commitment to full implementation of the International Health Regulations (2005) and, in particular, to accelerate action by and support for West and Central African States and other at-risk States, and furthermore commends in this regard North–South, South–South, triangular and bilateral cooperation and exchange of best practices;

30. URGES Member States,[1] supported by WHO, to work across sectors and stakeholders, including education, transport and regulatory systems, to ensure that preparedness and long-term sustainable capacity to prevent, detect, protect against, control, and provide a public health response to, the international spread of disease is embedded in communities and can facilitate community mobilization in case of an emergency with health consequences;

31. RECOGNIZES that global preparedness needs continuous commitment to research and development, reliance on a multisectoral approach, strengthening of health systems, economic development in developing countries and improved health status;

[1] And, where applicable, regional economic integration organizations.

32. FURTHER RECOGNIZES the importance of timely sharing of information on diagnostic, preventive and therapeutic products registered at the national or regional level, among Member States,[1] under the auspices of WHO, and the routine evaluation of the effectiveness of such products for the purpose of their timely use in response to an epidemic and requests the Director-General to provide, to the Executive Board at its 138th session, options for strengthening such information sharing, and for enhancing WHO's capacity to facilitate access to these products, including the establishment of a global database, starting with haemorrhagic fevers;

Therapeutic drugs and vaccines

33. RECOGNIZES the good progress made to date, under the leadership of the WHO in the process of developing Ebola vaccines and requests the Director-General to ensure the sustainability of the working groups on therapeutic drugs and vaccine clinical trial designs while they are needed, to ensure continued progress in the development of quality, safe, effective and affordable vaccines and treatments, while emphasizing the importance of completing WHO's work on emergency regulatory mechanisms and procedures ensuring patient safety, committing results of this work to the most affected countries in West Africa as a first priority, with an accompanying distribution and financing plan, to be communicated to Member States[1] as soon as it is ready;

34. REQUESTS the Director-General to evaluate the current status of the epidemic and to disseminate information as to the most critical research studies to complete; and requests the Director-General in consultation with technical experts and Member States'[1] regulatory agencies to develop guidance on the value and limitations of the data obtained from the clinical trials, giving particular attention to ethics, quality, efficacy and safety;

Ensuring WHO's capacity to prepare for and respond to future large-scale and sustained outbreaks and emergencies

35. AFFIRMS that a primary goal in reforming WHO's capacity to respond to future large-scale and sustained outbreaks and emergencies is to enable the Organization to support and/or build Member States'[1] capacity to prevent, detect, prepare for and respond to such outbreaks and emergencies;

WHO's structure and human resources

36. REAFFIRMS that all relevant WHO authorities with respect to administration, deployment and other human resource matters concerning preparedness, surveillance and response rest with the Director-General for outbreaks and emergencies with health consequences, and shall be exercised in a manner consistent with the principles and objectives of WHO and its Emergency Response Framework;

37. REQUESTS the Director-General to strengthen the emergency operational capabilities of the Organization to enable it to fulfil its constitutional mandate and respond to emergencies with health consequences on the basis of an all-hazards approach;

[1] And, where applicable, regional economic integration organizations.

38. UNDERLINES that it is essential in respect of the health emergency response that the Organization be capable of delivering on the complex and varying scale of health emergency response, emphasizing in particular systems for human resources, resource mobilization and financing, planning and information management, and ensuring unambiguous leadership and a coherent approach towards outbreak and health emergency operations for all levels of the Organization;

39. RECOGNIZES that, among others, the shortcomings in WHO's human resources systems and processes slowed down the response to Ebola virus disease, and requests the Director-General based on lessons learnt and taking into account the current reform efforts, to accelerate WHO's efforts on human resources reform, particularly by implementing at all three levels of the Organization robust recruitment and performance management, including performance review and mobility policies by the end of 2015 in order to rapidly match staff skills to urgent needs and to report to the Sixty-eighth World Health Assembly on plans for implementation and further expansion, taking into account the interim assessment requested in paragraph 52;

40. REQUESTS the Director-General to review the system for nomination, selection, training, and the performance review and improvement plan of WHO country representatives, taking into account, and without prejudice to, current reform efforts, with a view to improving expertise in each of the three core areas of WHO's mandate – normative work, technical support to countries, and emergency and outbreak response – and supports the Director-General in exercising her authority to add or change staff with appropriate expertise at the country and regional level, and to report on implementation to the Executive Board at its 138th session;

41. STRESSES the importance of WHO personnel understanding and respecting national and local customs and traditions in their countries of assignment and communicating clearly their purpose and objectives to local populations in order to enhance their acceptance, thereby contributing to their safety and security;

42. RECALLS recommendation 12 of the 2011 IHR Review Committee contained in document A64/10, which called for the establishment of a more extensive global, public health reserve workforce, and requests the Director-General to take immediately the necessary steps to draw up her plan in consultation with Member States through regular informal consultations, and with the Steering Committee of the Global Outbreak Alert and Response Network, with the following three elements, each of which are composed of comprehensive emergency response teams that can be promptly and efficiently deployed, for service in countries that request or accept such assistance, for adequate periods of time, and with adequate resources, and to report to the Sixty-eighth World Health Assembly for its consideration and decision:

(a) adequate numbers of dedicated and trained WHO staff with appropriate range of skills positioned at all levels of the Organization, particularly at country level, to properly implement ongoing emergency relief programmes, including surveillance, and to provide adequate internal surge capacity to respond to acute emergencies with health consequences, with efforts made to enhance representation from developing country practitioners, including at WHO headquarters;

(b) deepened and expanded partnerships building on existing platforms, notably the Global Outbreak Alert and Response Network, the Global Health Cluster, existing and new stand-by partners, and foreign medical teams, with the additional aim of building capacity in countries;

(c) strengthened mechanisms for working with other United Nations agencies, funds and programmes, and relevant actors, as appropriate, to assist in assuring a response commensurate to the scale of any emergency;

Research and development

43. RECOGNIZES the urgent need to encourage and maximize efforts on scientific, epidemiological and biological research, including the sharing of samples and epidemiological data in accordance with national or regional legislation on Ebola, and on health technologies and promote cooperation in this field between countries, as a contribution to international efforts directed towards tackling the epidemic and for the aim of consolidating the scientific, medical and health capacities of the most affected countries, and the need for the global community to continue work on research and development, including for emerging and neglected tropical diseases;

44. FURTHER RECOGNIZES WHO's leadership role in supporting a prioritized research agenda for Ebola and calls on Member States[1] and relevant actors to ensure that resources and efforts take into account and support, as appropriate, the prioritized research agenda;

45. FURTHER RECOGNIZES the need to incorporate lessons learnt from the outbreak of Ebola virus disease into the evaluation of the global strategy and plan of action on public health, innovation and intellectual property; considers, as appropriate, the linkage to pooled funds for global health research and development to facilitate the development of quality, safe, effective, affordable health technologies related to the needs of affected countries; and calls on Member States[1] to secure sustainable financing for health research and development on emerging and neglected tropical diseases, including Ebola, and enhance access to health products and medical devices to address the health needs of developing countries;[2]

46. CALLS ON Member States[1] to continue to collaborate as appropriate, on models and approaches that support the delinkage of the cost of new research and development from the prices of medicines, vaccines, and other diagnostics for Ebola and other emerging and neglected tropical diseases, so as to ensure their sustained accessibility, affordability, availability, and access to treatment for all those in need;

Resources

47. REQUESTS the Director-General to take all necessary steps to ensure that, in the case of outbreaks and emergencies with health consequences, funding can be speedily reallocated and disbursed to areas of most need, without compromising the Organization's programme priorities;

48. RECOGNIZES the need for adequate resources for the preparedness, surveillance and response work of WHO, agrees in principle to establish a contingency fund, taking into account recommendation 13 of the 2011 IHR Review Committee contained in document A64/10, subject to a decision to be taken by the Sixty-eighth World Health Assembly, and requests the Director-General to provide options on the size, scope, sustainability, operations and sources of financing for such a fund, and accountability mechanisms, including on possible internal sources of funding from within WHO's existing Programme budget, taking into account other relevant financing mechanisms and emergency

[1] And, where applicable, regional economic integration organizations.

[2] See resolutions WHA61.21, WHA62.16 and WHA66.22.

funds already in operation or being considered, at regional and global level, taking into account the interim assessment requested in paragraph 52 and to report on such options, through the Programme, Budget and Administration Committee, to the Sixty-eighth World Health Assembly for its consideration and adoption;

49. FURTHER RECOGNIZES the valuable contribution to global capacity to prevent, detect and respond to future outbreaks being made through various initiatives at global and regional levels and other relevant actors, and calls on these efforts to be aligned with the International Health Regulations (2005) and the relevant work of WHO, to ensure coherence and effective action;

50. URGES Member States[1] to consider supporting and contributing to WHO work in this area as a matter of urgency;

Communication

51. REQUESTS the Director-General to continue to develop and implement an Organization-wide communications strategy to improve routine communications, messaging about preventive measures, risk communication, and emergency communications, ensuring that the new policy entails matching the content, form and style of communication with the media, timing and frequency that will reach the intended audience and serve its intended purpose;

Evaluation and next steps

52. REQUESTS the Director-General to commission an interim assessment, by a panel of outside independent experts, on all aspects of WHO's response, from the onset of the current outbreak of Ebola virus disease, including within the United Nations Mission for Ebola Emergency Response, in implementing the WHO's Emergency Response Framework, and in coordination, including resource mobilization, and functioning at the three levels of the Organization, to be presented to the Sixty-eighth World Health Assembly;

53. FURTHER REQUESTS the Director-General to prepare options for establishing an IHR Review Committee panel of experts pursuant to past practice to conduct an assessment of the overall prevention, preparedness and response to the outbreak of Ebola virus disease and the effectiveness of the International Health Regulations (2005) in facilitating that response, including what was implemented and what was not from the previous IHR Review Committee in 2011, and consideration given to steps that could be taken to improve the functioning, transparency, and efficiency of WHO's response under the International Health Regulations (2005) in future outbreaks, in all countries, aiming at strengthening health systems;

54. INVITES the Director-General to consider the establishment of an ad hoc advisory group under the auspices of the Executive Board, composed of operations experts from relevant stakeholders, including affected countries, to provide advice on administrative and logistical support to the Director-General as needed in the case of future outbreaks or emergencies with health consequences;

55. REQUESTS the Director-General to engage within the United Nations system on lessons learnt from this response for improving coordination and effectiveness for future outbreaks, and to update Member States[1] on a regular basis;

[1] And, where applicable, regional economic integration organizations.

56. FURTHER REQUESTS the Director-General to consult with Member States,[1] other relevant actors, and the United Nations system on elements of the decisions included in this resolution to be prepared for the Sixty-eighth World Health Assembly with a view to ensuring a consensus on how to strengthen and improve the effectiveness of WHO in outbreaks and emergencies with health consequences and taking into account, and without prejudice to, the overall WHO reform;

57. FURTHER REQUESTS the Director-General to report to the Sixty-eighth World Health Assembly on all grade 3 and United Nations Inter-Agency Standing Committee level 3 emergencies where WHO has taken action since the Sixty-seventh World Health Assembly and calls for annual reports on WHO's actions in health emergency response.

Second meeting, 25 January 2015
EBSS3/SR/2

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[1] And, where applicable, regional economic integration organizations.

World Health Organization

EXECUTIVE BOARD
136th session
Provisional agenda item 9.3

EB136/25
12 December 2014

Global vaccine action plan

Report by the Secretariat

1. In May 2012, the Sixty-fifth World Health Assembly endorsed the global vaccine action plan[1] and requested the Director-General to monitor progress and report annually, through the Executive Board, to the Health Assembly, until the Seventy-first World Health Assembly, on progress towards achievement of global immunization targets, as a substantive agenda item, using the proposed accountability framework to guide discussions and future actions.[2]

2. In May 2013, the Sixty-sixth World Health Assembly noted the report by the Secretariat,[3] including the proposed framework for monitoring and evaluation and accountability, as well as the process for reviewing and reporting progress under the independent oversight of the Strategic Advisory Group of Experts on immunization.[4]

3. In accordance with the monitoring, evaluation and accountability process,[5] the Strategic Advisory Group of Experts on immunization reviewed progress against each of the indicators for the goals and strategic objectives of the global vaccine action plan, based on data from 2013, and prepared the 2014 Assessment Report of the Global Vaccine Action Plan.[6]

4. A summary of the 2014 Assessment Report by the Strategic Advisory Group of Experts on immunization is included in the Annex.

ACTION BY THE EXECUTIVE BOARD

5. The Executive Board is invited to take note of the report and to consider the recommendations for actions to be taken by the various stakeholders of the global vaccine action plan, in particular by Member States.

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[1] The global vaccine action plan can be found at: http://www.who.int/immunization/global_vaccine_action_plan/en/ (accessed on 19 November 2014).

[2] Resolution WHA65.17.

[3] Document A66/19.

[4] See document WHA66/2013/REC/3, summary record of the tenth meeting of Committee A, section 2.

[5] See document A66/19, paragraphs 16 and 17.

[6] The 2014 Assessment Report of the Global Vaccine Action Plan is posted at: http://www.who.int/immunization/global_vaccine_action_plan/sage_assessment_reports/en/ (accessed on 24 November 2014).

ANNEX

A SUMMARY OF THE 2014 ASSESSMENT REPORT OF THE GLOBAL VACCINE ACTION PLAN BY THE STRATEGIC ADVISORY GROUP OF EXPERTS ON IMMUNIZATION

1. The Global Vaccine Action Plan (GVAP) has two great ambitions, to make 2011–2020 the Decade of Vaccines:

- To deliver vaccination to all – and through this: to end inequity in vaccination, eradicate polio globally, eliminate maternal and neonatal tetanus globally, and eliminate (guided by regional targets) measles and rubella.

- To unleash vaccines' vast future potential – because their impressive history is nothing in comparison to what they could yet achieve.

2. The Strategic Advisory Group of Experts on immunization noted that there has been success in introducing new vaccines, and positive achievements in numerous countries in several areas, including the establishment and strengthening of National Immunization Technical Advisory Groups. However, progress is far off-track. Five of the six goals set by the GVAP with deadlines at the end of 2014 or 2015 still require substantial progress to get the goals on track (poliovirus transmission interruption, maternal and neonatal tetanus, measles and rubella elimination, and DTP3 coverage targets). Indeed, most have seen very little progress. Some have been missed multiple times before.

3. To get the Action Plan back on track, the Strategic Advisory Group of Experts on immunization recommends that action focus particularly on addressing five priority problems. Each problem is major, but each can be tackled, with a reasonable expectation that doing so will improve progress considerably. Each problem is detailed in the full 2014 Assessment Report of the Global Vaccine Action Plan[1] of the Strategic Advisory Group of Experts on immunization, and is summarized below.

Weak GVAP implementation

4. Three years after its start date, implementation of the GVAP is patchy and slow. All countries and organizations that have committed to this endeavour should re-examine the level and nature of their contributions, and urgently make the improvements necessary to achieve results.

5. The Strategic Advisory Group of Experts on immunization recommends that:

- The Director-General of WHO, during the Sixty-eighth World Health Assembly in 2015, convene side meetings in collaboration with the GVAP secretariat agencies for countries with routine vaccination (DTP3) coverage of less than 80%, to which each Minister of Health is asked to report on the challenges, plans and timelines to improve coverage to meet the GVAP goals.

[1] http://www.who.int/immunization/global_vaccine_action_plan/en/.

- Partners are called upon to lead a concerted effort to fill the funding gap and scale up advocacy efforts to achieve the neonatal (and maternal) tetanus elimination target by end 2015.

- Regions and countries rapidly finalize their own vaccine action plans based on the GVAP, using this assessment report as a further guide and establishing bodies to guide and monitor implementation.

- Following adoption of the GVAP and subsequent revision and adoption of regional and national plans, countries have the responsibility to ensure that immunization goals are shared, discussed and fully adopted by health care workers.

- Countries give civil society organizations substantially more formal involvement in the delivery and improvement of vaccination services, establishing clear responsibilities for which they are accountable.

- After consulting with the respective Regional Technical Advisory Group, every region establishes a regional verification commission, and after consulting with the respective National Immunization Technical Advisory Group, every country explores options for establishing a national verification commission, to scrutinize and monitor progress towards the measles elimination targets.

- The heads of the GVAP secretariat agencies (the Bill & Melinda Gates Foundation, GAVI The vaccine alliance, the National Institute of Allergy and Infectious Diseases, WHO and UNICEF) meet to consider this report and to agree on specific corrective actions.

- The heads of GVAP secretariat agencies report to the 2015 World Economic Forum in Davos on the plan's establishment, its lack of progress so far and what forum participants – who supported the Decade of Vaccines concept in 2010 – can do to help its implementation.

- The SAGE's GVAP assessment reports remain as standing items at the World Health Assembly until 2020.

Poor data quality and use

6. Poor quality and use of data is substantially impeding programme management and improvement.

7. The Strategic Advisory Group of Experts on immunization recommends that:

- Countries invest in improving data quality at the local level, and use data to strengthen accountability and to improve understanding of what the programmatic issues are.

- Technical agencies further develop and deploy tools to help countries with the practical task of improving the quality and use of data, with limited personnel available to do so.

Vaccine affordability and supply

8. The affordability and supply of vaccines need to be urgently examined. Each may be causing a significant problem for a large number of countries, and the current lack of proper information hinders understanding and corrective action.

9. The Strategic Advisory Group of Experts on immunization recommends that:

- Technical agencies conduct urgent assessments of (i) the extent to which the reported national-level stock-outs are affecting local vaccine supply and delivery, and (ii) the root causes of these stock-outs.

- Countries are requested to change the rules of the game on vaccine affordability, to create transparency which is in their interest. They can do this by making pricing information publicly available, and by collaborating with WHO and all technical agencies to develop solutions.

- Technical partners support countries to improve the transparency of vaccine pricing. Technical agencies themselves should do everything possible to share pricing data.

Failures of basic integration

10. Failures of basic integration mean that health care workers are repeatedly missing easy opportunities to offer vaccinations when people attend clinics with other problems.

11. The Strategic Advisory Group of Experts on immunization recommends that:

- Countries conduct studies to understand how opportunities to vaccinate people are being missed by health care workers and their systems, and act to reduce the incidence.

- WHO discusses and develops guidelines on how to fully integrate vaccination into the operation of all aspects of the health care system and to reduce missed opportunities to vaccinate.

- Countries ensure that health care workers understand and follow WHO or national guidelines on what does, and does not, contraindicate vaccination, particularly in relation to childhood febrile illness, so that vaccination is not avoided unnecessarily.

Situations disrupting immunization

12. Vaccine delivery is impeded by disruptive situations, including war and major disease outbreaks (such as Ebola, currently). Such situations will always exist. Vaccines must be delivered despite them.

13. The Strategic Advisory Group of Experts on immunization recommends that WHO expand its existing guidance on immunization in humanitarian emergencies to detail how routine and other immunization services are best maintained despite disruptive situations, such as war and disease outbreaks.

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WHO 136th EXECUTIVE BOARD
GLOBAL VACCINE ACTION PLAN, Document 136/25,
AGENDA ITEM 9.3, Geneva, 26th January 2015
SUMMARY OF THE SESSION

Twenty-seven speakers including 22 representatives from Member States[1] (i.e. 16 Executive Board Members and 6 non-Executive Board Members), four civil society organizations[2] and one pharmaceutical manufacturer association[3] took the floor during the discussion on the Global Vaccine Action Plan (GVAP).

Delegates commended the Strategic Advisory Group of Experts (SAGE) on immunization for an excellent assessment report[4] and took note of the recommendations.

While Member States acknowledged successes in a few areas, most notably the reduction of polio cases in 2014 in the African region, they took note of the fact that we are not on track to meet 5 of the 6 targets for 2014-15. They highlighted the need for all stakeholders, particularly national governments and technical partners, to make the needed investments and efforts to ensure that GVAP targets are achieved.

Delegates highlighted several issues that they felt needed to be addressed if the global immunization goals are to be achieved including:

- Increasing coverage for routine immunization, focusing on strengthening health systems and addressing inadequacies in the health workforce;
- Providing clear guidelines and support for sustaining immunization programmes when health services are affected due to conflict, civil unrests, or disease outbreaks;
- Ensuring countries have access to sustainable supply of vaccines at affordable prices;
- Access to sustainable financing of immunization programme, especially in countries as they graduate out of Gavi support;
- Enhancing the quality of immunization data and to establish processes such as through strengthening National Immunization Technical Advisory Groups (NITAGs) to enable evidence-informed decisions on policies and strategies.

There was strong support from Member States for the SAGE recommendation to convene a special meeting during the upcoming World Health Assembly to discuss how best technical partners and donors can provide support in tackling the challenges facing countries with low vaccination coverage rates.

In its response, the WHO secretariat, while taking note of all the issues raised by the delegates emphasized the need for collective and cohesive action by all immunization stakeholders, including Member States, to get back on track towards achieving the global immunization targets and reaffirmed WHO's commitment in supporting this process.

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[1] Kuwait, Malaysia, DR Congo, Croatia, Cuba, China, Australia, Lebanon, USA, Russia, Iran, Saudi Arabia, Panama, DPR Korea, Brazil, Argentina, Canada, Colombia, Thailand, Mexico, Germany and Lybia

[2] International Pharmaceutical Students´ Federation (IPSF), MSF, Medicus Mundi International – International Organisation for Cooperation in Health Care (MMI), Save the Children

[3] International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)

[4] EB136, 136/25, Agenda Item 9.3, http://apps.who.int/gb/ebwha/pdf_files/EB136/B136_25-en.pdf

WHO 136th EXECUTIVE BOARD
GLOBAL VACCINE ACTION PLAN, ITEM 9.3
Geneva, 26th January 2015
COUNTRIES AND NGOs INTERVENTIONS
INFORMAL SUMMARY RECORDS
(not to be shared)

1. **Kuwait**
   - Supports the recommendations that further work and investments are needed to strengthen immunization programmes in the low coverage countries
   - Highlights the importance of data quality, the role NITAGs can play in monitoring progress towards GVAP targets at national levels;
   - Notes the impact of conflict on immunization coverage, including the impact of recent increase of refugees in the region (including financial burden this imposes on the host countries, given the high price of vaccines) and highlight the need for WHO guidance on how to sustain coverage during conflicts and crisis. including
   - Supports the recommendations to convene a technical side meeting at the next WHA on accelerating progress in low coverage countries

2. **Malaysia**
   - Highlights the importance to share the GVAP vision with all health care staff at all levels to obtain their commitment in implementing and achieving the targets.
   - Requests WHO to provide more support on how countries should deal with anti-vaccines lobbies (communication strategies to increase individuals and communities demand for immunization)
   - Introduction of new vaccines should be based on local data and health priorities.
   - Anti-vaccine movement social media – communication strategies to be one of the items in the agenda of the GVAP

3. **Democratic Republic of the Congo**
   - Statement on behalf of all AFR Countries
   - Highlights that indeed GVAP targets are not on track to be achieved, DTP3 coverage rates in AFR is still low (around 75-78%), below the target set;
   - However some progress has been made in our region controlling polio (no cases for 6 months); introducing new vaccines (October 2014, PCV in 31 MS, rotavirus vaccine in 22 countries but HPV vaccines in only 4 countries and Men A CV in 13 countries)
   - Ebola outbreaks are disrupting for health services (including immunization) in Guinea, Liberia, SL, and also in Mali, Nigeria, Senegal and DRC.
   - The Regional Strategic Regional Plan 2014-2020 has been endorsed by the Task Force on Immunization (TFI) and adopted at the Regional Committee. Main challenges will be to strengthen routine immunization, the health system and the financial sustainability for immunization programs.
   - There is a need to ensure better coordination mechanisms in countries so that everyone agrees on the priorities set by the Ministry of Health(MoH) and better use the financial resources.
   - Rehabilitation of health systems, competent trained skilled staff to provide health care to vulnerable groups and even physical rehabilitation of hospitals and health care centres
   - Capitalize from positive experiences from countries is important (supplementary immunization activities, immunization conducted between neighbouring countries)

4. **Croatia**
   - European Regional Vaccine Action plan has been adopted by the Member States with 6 objectives; Croatia supports both the GVAP and the EVAP.
   - Croatia is meeting all the GVAP goals, including interruption of transmission of polio and measles, hepatitis control, sustaining high coverage and evidence-based decision making
   - However sustainability of achievements is difficult because of the financial sustainability due to austerity measures linked to the economic crisis
   - Difficulties in timely procurement of vaccines due to global shortage of vaccines
   - Challenges related to a vaccine uptake due to anti-vaccine movement: WHO is requested to play a stronger role.
   - Request WHO to mediate between vaccine manufacturers and the Member States to ensure access to sustainable supply of vaccines at affordable prices.

5. **Cuba**
   - Trying to eliminate maternal and neonatal tetanus (MNT), polio, rubella, measles, combat hepatitis B
   - Ensuring accessibility to safe vaccines is crucial and involves both public and private manufacturers (including developing countries producers)
   - Solid financing is needed for vaccination programmes in the context of the universal health coverage (UHC) and the important role of immunization

6. **China**
   - Commend the active actions in pushing the GVAP
   - The report objectively reports the progress and the difficulties faced.
   - .
   - Implementation of GVAP requires an extensive collaboration between WHO, Member States and partners to exchange technology.
   - WHO to mobilize more resources, increase accessibility and equity
   - Civil Society Organizations (CSOs) should respect the countries' regulation and WHO should not provide uniform rules for this collaboration.

7. **Australia**
   - Supports routine immunization as a crucial element of the investment in improving child health.
   - Support to increase routine immunization coverage rates is a core business for WHO and an important indicator of the Organization performance at country level.
   - Put sustainable finance at the heart of the discussion especially in Gavi graduating country.
   - Progress is "Slow and patchy" as noted in the report, WHO and partners (UNICEF) should indeed prioritize countries with "less than 80% coverage" for more intensive support.
   - There is a need for review and support to strengthen routine immunization in some Pacific island states where immunization rates are very low.

8. **Lebanon**
   - Need to focus on low coverage countries to discuss issues, funding gaps and implementation obstacles.
   - Supports the recommendations to convene a side technical meeting at the next WHA on low coverage countries and gather the views of the ministers on the challenges their countries face.
   - Welcome the recommendation for specific guidance for countries facing war and conflicts Lebanon is providing the same immunization services to Syrian refugees as for Lebanese nationals, thanks to the support from the MoH and CSOs. However, the burden is heavy especially financially (due to the high prices of pneumococcal or rotavirus vaccines). This has created some delays in providing those vaccines to refugees.

9. **USA**
   - Make polio eradication a focus.
   - Great progress despite the security challenges: no reported case in the last 6 months in the African Region and 9 months in the Middle East.
   - Surveillance needs to be strengthened.
   - If polio transmission is not interrupted in Pakistan, there is a global risk which can cost another US$1 billion a year for polio eradication efforts worldwide.
   - The world needs to be prepared for the timely switch from tOPV to bOPV.
   - Routine immunization needs to be strengthened for the successful implementation of the end game.

10. **Russia**
   - Agree with the challenges highlighted by SAGE in their report, based on a systematic review.
   - There is a need for stable financing for national immunization programmes, a problem for low middle income countries (LMICs).
   - Russia's contribution to eradicate polio and eliminate measles and rubella in neighbouring countries.
   - Highlights the importance of data quality and of strong health systems
   - Need also to support countries to ensure immunization services during crisis

11. **Iran**
   - WHO to help support MS to achieve the GVAP goals.
   - Monitoring and evaluation is very important; it is recommended that NITAGs should be established and supporting these activities of monitoring and verification of objectives achievements (by also ensuring CSOs, Academics are involved).
   - Prioritize reaching migrant and remote populations; Iran is making special efforts.
   - Countries should be supported to strengthen capacity for rapid response to disease outbreaks.
   - Universal access to vaccines, affordability, and transparency of prequalification processes are important in reaching the GVAP.

12. **Saudi Arabia**
   - Endorsed statements by Member States from the region.
   - Reported some technical issues related to the online access to the report

13. **Panama**
   - Reports the existence of a national law for immunization which includes the existence of specific budget lines
   - Highlights the importance of financial sustainability
   - Extended the number of vaccines offered free of charge.
   - Extra resources were set aside to cover for additional cost linked to new vaccines
   - Expressed the need to be flexible with global targets to accommodate national priorities and to reflect regional differences.

14. **DPR of Korea**
   - Efforts were done to maintain high coverage for all antigens with WHO and UNICEF support
   - Highlights the issues related to vaccines affordability (and the cost of vaccines)

15. **Brazil**
   - Congratulates SAGE and supports their recommendations; agrees with the focus on data quality

- Gavi and the AMRO Revolving fund should continue to play a role to guarantee universal access to vaccines.

16. **Argentina**
    - Reports its own achievement (DTP3 80% coverage in all provinces, introduction of new vaccines, diseases eliminations).
    - Data quality achieved thanks to integrated systems throughout the country and electronic reporting tools
    - AMRO revolving fund to ensure vaccines are available at the lower prices
    - Need to increase local production of vaccines and producers in MICs
    - Problems in terms of prices and availability of vaccines, producers to show flexibility so that we can ensure our immunization programme are going on.

17. **Canada**
    - Commends the report, though concerned about lagging progress; supports SAGE recommendations.
    - Priorities, risk (mitigation) and role of partners for the upcoming years must be outlined in future reports.
    - Show in the report how efforts are tied to results and to the overall system strengthening
    - Importance of affordable vaccines and possible role of tiered pricing
    - Need to understand the leadership roles of implementing agencies and whether there are dedicated funds to implement the recommendations.

18. **Colombia**
    - Concern about prices and cost for acquisition of vaccines. They account for a consistent part of the health budget. Support the recommendation on sharing information on pricing.
    - Supports the recommendations to convene a side technical meeting at the next WHA on low coverage countries

19. **Thailand**
    - Strong health systems are crucial to increase and maintain high immunization coverage.
    - There is an important issue related to workforce insufficiency (availability and training). HCW migrate, shift positions or tasks. Lack of strong management teams is a structure barrier. WHO should provide some support to MS in this area.
    - Financial sustainability is the other main issue. Access to immunization are at threat: need to expend national production, strengthen NRAs, and regional collaboration for ensuring vaccine security. WHO should support these projects.

20. **Mexico**
    - Endorses and commends the GVAP report.
    - Universal coverage is a priority
    - Introduction of new vaccines should be done in a responsible fashion.

21. **Germany**
    - Supports all recommendations made in the report.
    - Specifically support the recommendation to foster integration to reduce missed opportunities.
    - Reference made to the GAVI replenishment conference to be held in Berlin the 27 January 2015.

22. **Libya**
    - Problems with availability of vaccines in a big part of the country due to the current conflict (security issues for HCW)

- What can WHO do to help, shall we wait for polio cases for WHO to intervene?

23. **MSF**
    - See attached statement.
    - Along the lines of their recent press release and focused on vaccine prices

24. **Medicus Mundi International**
    - See attached statement.
    - Comment related to the vertical nature of immunization programmes, which could be to the detriment of strengthening primary health care in general.

25. **International Pharmaceutical Federation**
    - See attached statement.
      Raised the need to increase awareness and community demand.

26. **IFPMA**
    - See attached statement
    - Express commitment to GVAP and to country self-sufficiency

27. **Save the Children**
    - See attached statement.
    - Concerned about lack of progress and emphasized that immunization should be viewed as the flagship for universal coverage.

World Health Organization
REGIONAL OFFICE FOR Africa

AFR/RC64/R4
7 November 2014

REGIONAL COMMITTEE FOR AFRICA **ORIGINAL: ENGLISH**

Sixty-fourth session
Cotonou, Republic of Benin, 3-7 November 2014

RESOLUTION

REGIONAL STRATEGIC PLAN FOR IMMUNIZATION 2014–2020

(Document AFR/RC64/5)

The Regional Committee,

Having carefully examined Document AFR/RC64/5 entitled "Regional Strategic Plan for Immunization 2014–2020";

Recognizing the importance of immunization as one of the most cost-effective interventions in public health;

Reaffirming resolution WHA 65.17 that commits Member States to apply the vision and strategies of the Global Vaccine Action Plan (GVAP) and to allocate adequate human and financial resources to achieve vaccination goals;

Noting that, although there has been some progress in improving routine vaccination coverage in the African Region during the period 2006–2009, a significantly high number of children are still missed every year and should be vaccinated if the agreed regional and global targets are to be met;

Concerned that the current levels of national budgetary allocation to vaccination programmes cannot sustain the progress made in the introduction and scaling up of new vaccines that are more expensive than the traditional vaccines;

Having considered the proposed strategies for accelerating the achievement of EPI goals for the period 2014–2020;

1. ENDORSES Document AFR/RC64/5 entitled *Regional Strategic Plan on Immunization 2014–2020*;

2. URGES Member States:

(a) to develop and implement comprehensive multi-year plans (cMYPs) with integrated annual operational plans in line with the Global and Regional Vaccination Plans;

(b) to commit themselves to allocating adequate human and financial resources to achieve the vaccination goals and other relevant key milestones;

(c) to mobilize, involve and empower communities to effectively demand and utilize vaccination services;

(d) to enhance and sustain multisectoral collaboration and partnerships in the implementation of key approaches;

3. REQUESTS the Regional Director:

(a) to provide the necessary technical support to Member States for the development, and implementation of cMYPs as well as annual operational plans in order to achieve the set objectives and targets;

(b) to develop, in consultation with Member States, monitoring, evaluation and accountability mechanisms for the implementation of the Regional Strategic Plan for Immunization 2014–2020;

(c) to foster continued collaboration with international and multilateral agencies, donor organizations and EPI partners to harmonize policies and efficient and sustainable utilization of resources;

(d) to report to the Regional Committee beginning in 2015 and thereafter every year on the progress made, remaining challenges and updated actions towards the achievement of the set objectives and targets.

World Health Organization
REGIONAL OFFICE FOR Africa

AFR/RC64/PSC/3
3 June 2014

REGIONAL COMMITTEE FOR AFRICA **ORIGINAL: ENGLISH**

PROGRAMME SUBCOMMITTEE

Sixty-fourth session
Brazzaville, Republic of Congo, 9–11 June 2014

Provisional agenda item 5

REGIONAL STRATEGIC PLAN FOR IMMUNIZATION 2014–2020

Report of the Secretariat

EXECUTIVE SUMMARY

1. Immunization is considered as one of the most cost-effective public health interventions. Regional coverage with three doses of Diphtheria-Tetanus-Pertussis containing vaccine and the first dose of Measles Containing Vaccine were maintained around 70% during the last three years. There has been an estimated 88% reduction in measles mortality since 2000 and only one country in the Region remains endemic for wild poliovirus.

2. External evaluation of the 2009–2013 Regional Immunization Strategic Plan revealed challenges that hinder access and utilization of immunization services. These include gaps in organization, coordination and management of immunization activities, inadequacy of vaccines and cold storage capacity, limited service delivery points, and inappropriate communication strategies resulting in low community awareness and participation.

3. One of the significant developments in the field of immunization is the Global Vaccine Action Plan that needs implementation in the Region. The Regional Immunization Strategic Plan 2014–2020 is intended to address the identified challenges by providing policy and programmatic guidance to Member States within a strong national health system and also during humanitarian emergencies.

4. The key approaches include integrating immunization into national health policy and plan and during emergencies, strengthening financing, enhancing partnerships, building national capacity, improving monitoring and data quality, improving vaccine management, safety and regulation and promoting implementation, research and innovations.

5. The Regional Committee is invited to review the Regional Immunization Strategic Plan 2014–2020 and endorse the actions proposed.

CONTENTS

INTRODUCTION

1. Immunization is considered as one of the most cost-effective public health interventions. Globally, an estimated 2.5 million child deaths and 600 000 adult deaths are prevented annually through immunization.

2. In 2010, the Sixtieth WHO Regional Committee for Africa adopted a resolution,[1] urging Member States to integrate immunization into national health development policy and plans, and to increase financing. The Regional Committee has also institutionalized an annual African Vaccination Week for sustaining advocacy, expanding community participation and improving service delivery.

3. In 2011, the Sixty-first session of the Regional Committee adopted a resolution[2] for measles elimination by 2010. The resolution urged Member States to provide adequate resources for the implementation of national plans to sustain the gains in measles mortality reduction.

4. In 2012, the Sixty-fifth World Health Assembly endorsed the Global Vaccine Action Plan (GVAP).[3] The GVAP is a strategic framework that aims to realize the full potential of immunization during the Decade of Vaccines 2011–2020. It commits Member States to develop the immunization component of their national health strategy and plans, and allocate adequate resources to achieve the immunization goals.

5. Subsequently, in May 2013, the Sixty-sixth World Health Assembly discussed the Polio Eradication and Endgame Strategic Plan, 2013–2018. This plan has four main objectives: (a) detection and interruption of any poliovirus transmission; (b) strengthening of immunization systems and withdrawal of Oral Polio Vaccine; (c) containment of all polioviruses and certification; and (d) development of a comprehensive legacy plan.

6. In June 2013, an external evaluation of the 2009–2013 Immunization Strategic Plan reported that there has been substantial progress especially a significant decrease in the number of wild poliovirus (WPV)[4] cases and prompt massive introduction of conjugate meningococcal A meningitis vaccine (MenAfriVac™) in the African meningitis belt, with a considerable impact on the annual meningitis epidemics and a significant reduction of measles mortality.

7. However, several challenges were identified, including inadequacy and sustainability of financing, weakness of the health workforce and limited access to service delivery. In addition, interventions were not implemented at full scale; procurement and supply chain systems were weak, low community engagement was low in addition to weak surveillance of vaccine-preventable diseases.

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1 Resolution AFR/RC60/R4, Current status of routine immunization and polio eradication in the African Region: challenges and recommendations. In: *Sixtieth session of the WHO Regional Committee for Africa, Malabo, Equatorial Guinea, 30 August –3 September 2010, Final report,* Brazzaville, World Health Organization, Regional Office for Africa, 2010 (AFR/RC60/21) pp.14–17.

2 Resolution AFR/RC61/R1, Measles elimination by 2020: a strategy for the African Region. In: *Sixty-first session of the WHO Regional Committee for Africa, Yamoussoukro, Cote d'Ivoire, 29 August –2 September 2011, Final report,* Brazzaville, World Health Organization, Regional Office for Africa, 2011 (AFR/RC61/14) pp.7-8.

3 Resolution WHA65.17, Global Vaccine Action Plan.

4 274 WPV cases were reported in 2013 compared with 691 in 2009.

SITUATION ANALYSIS AND JUSTIFICATION

Situation analysis:

8. Immunization coverage with three doses of Diphtheria-Tetanus-Pertussis containing vaccine (DTP3)[5] and the first dose of Measles Containing Vaccine (MCV1)[1] for the Region has plateaued at around 70% in the past three years. Twenty-three[6] of the 31 countries at risk of yellow fever introduced the vaccine, with four countries[7] attaining 90% coverage in 2012.

9. Additional vaccines were introduced into national immunization schedules. All countries but one had introduced hepatitis B vaccine and *Haemophilus influenzae* type b vaccine as of December 2013. However, there has been a slow pace of introduction of new vaccines: pneumococcal conjugate vaccines (PCV) and rotavirus vaccines were introduced by 29[8] and 15[9] countries respectively while human papilloma virus (HPV) vaccine has been introduced only in Lesotho, Rwanda and South Africa.

10. More than 150 million people in 12 countries[10] have been vaccinated with MenAfriVac™ in campaigns since 2010, and no confirmed case of meningitis A has been identified among the vaccinated populations.[11] In 2013, a total of 87.8 million children received measles vaccination through Supplementary Immunization Activities (SIAs) in 16 countries.[12] Four[13] of these 16 countries conducted their follow-up SIAs using Measles-Rubella vaccine targeting children from 9 months to 14 years of age, thus pioneering the introduction of rubella vaccine in the Region. Through these efforts, the African Region achieved 88% reduction in estimated measles deaths between 2000 and 2012.[14] The elimination of maternal and neonatal tetanus was also validated in 30 countries[15] as of December 2013.

11. There has been a significant decrease in the number of wild poliovirus cases (WPV) in the Region. Furthermore, 128 WPV cases were reported in 2012 compared with 691 in 2009. Nigeria, the only country still endemic in the Region recorded nearly 70% reduction of confirmed WPV cases between 2009 (388 cases) and 2012 (122 cases). In 2013, Cameroon, Ethiopia and Kenya experienced outbreaks following an increase in importation of WPV1. The outbreaks in Cameroon and Ethiopia have persisted into 2014, and as of April 2014, a fourth country i.e. Equatorial Guinea had also confirmed polio outbreak following WPV importation.

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5 WHO-UNICEF national immunization coverage estimates.

6 Angola, Benin, Burkina Faso, Cameroon, Central African Republic , Chad, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Mali, Niger, Nigeria, Sao Tome and Principe, Senegal, Sierra Leone and Togo.

7 Côte d'Ivoire, Gambia, Ghana and, Sao Tome and Principe.

8 PCV: Angola, Benin, Botswana, Burundi, Burkina Faso, Cameroon, Central African Republic, Congo, Democratic Republic of Congo, Ethiopia, Gambia, Ghana, Kenya, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Rwanda, Sao Tome and Principe, Senegal, Sierra Leone, South Africa, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe.

9 Rotavirus vaccines: Botswana, Burkina Faso, Burundi, Cameroon, Congo, Ethiopia, Gambia, Ghana, Malawi, Mali, Rwanda, Sierra Leone, South Africa, Tanzania and Zambia.

10 Benin, Burkina Faso, Cameroon, Chad, Ethiopia, Gambia, Ghana, Mali, Niger, Nigeria, Senegal and South Sudan.

11 Data from the enhanced meningitis surveillance system.

12 Botswana, Cape Verde, Comoros, Congo, Democratic Republic of Congo, Ethiopia, Ghana, Lesotho, Madagascar, Malawi, Nigeria, Rwanda, Senegal, South Africa, Swaziland and Togo.

13 Cape Verde, Ghana, Rwanda and Senegal.

14 Global control and Regional elimination of measles. 2000–2012.Weekly Epidemiological Record No 6. 2014, 89, 45–52.

15 Algeria, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Comoros, Congo, Eritrea, Ethiopia, Gambia, Ghana, Guinea Bissau, Lesotho, Liberia, Malawi, Mauritius, Mozambique, Namibia, Rwanda, Senegal, Seychelles, South Africa, Swaziland, Tanzania, Togo, Uganda, Zambia and Zimbabwe.

12. Forty-one countries[16] had reported specific budget allocations for immunization in their national health budgets as of December 2012. Government funding for routine immunization increased, on average, from 43% in 2006 to 52% in 2010.

13 Surveillance networks targeting vaccine-preventable diseases (VPDs) have been established in the 47 countries in line with the Integrated Disease Surveillance and Response strategy and the International Health Regulations 2005. This has played a critical role in directing activities of national immunization programmes. Data generated from surveillance networks in the Region indicated a high prevalence of rotavirus diarrhoea, measles, rubella, and pneumonia.

14. Humanitarian emergencies that occurred recently in the Region,[17] regardless of the type or cause, have been associated with epidemics of diarrhoea, measles, meningitis, etc. Most of these diseases can be prevented through vaccination if anticipated by timely intervention.

Justification

15. Despite the progress made, many challenges remain to be addressed. An estimated 8 million children in the Region, 81% of whom live in 10 countries,[18] did not receive their DTP3 vaccine in 2012. There is a resurgence of measles and WPV outbreaks due to gaps in immunization coverage. The high cost of new vaccines poses a real challenge to middle-income countries that are not eligible for GAVI support.

16. The proposed new *Regional Strategic Plan for Immunization 2014–2020* is intended to provide policy and programmatic guidance to Member States, in line with the GVAP, in order to optimize immunization services including in emergencies.

STRATEGY FORMULATION

Priority setting

17. The enabling factors for good immunization performance and broad national commitment include local recruitment of, and provision of support to, community health workers; active community participation in immunization and health activities; partnership between health staff and local government authorities; focus on accountability and performance monitoring; and existence of essential immunization infrastructure[19] at all levels.

18. Reaching the un-served 20% of children represents the most daunting challenge for the Region. Some of the "one infant in five" who are not immunized live in "hard-to-reach" areas or in communities whose access to health services is limited. Others may be living very close to a health centre and yet may have been simply overlooked by the local health staff when microplans for community coverage were drawn up.

19. Making the best use of the available vaccines requires a renewed emphasis on, and prioritization of, routine immunization services – the platform on which all immunization activities can be mounted – within the context of health system strengthening, based on national decision-making.

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16 www.who.int/immunization/programmes_systems/financing/analyses/jrf_analysis/en/. Accessed on 13 March 2014.
17 Central African Republic, Mali and South Sudan.
18 Chad, Democratic Republic of Congo, Ethiopia, Kenya, Mali, Mozambique, Niger, Nigeria, South Africa and Uganda.
19 Justice J. et. al., Study of the drivers of routine immunization system performance in Ethiopia, JSI Research and training Institute Inc., ARISE Project for the Bill and Melinda Gates Foundation, 2012.

Aim, objectives and targets

20. The aim of the *Regional Immunization Strategic Plan 2014–2020* is to achieve universal immunization coverage within the WHO African Region.

21. The objectives are:

(1) To increase vaccination coverage.

(2) To complete the interruption of poliovirus transmission and ensure virus containment.

(3) To eliminate measles and advocate for the elimination of rubella and congenital rubella syndrome.

(4) To attain and maintain elimination/control of other vaccine-preventable diseases.

22. The targets are as follows:

Objective 1: To increase vaccination coverage.

(a) Reach DTP3-containing vaccine coverage of at least 90% region-wide by the end of 2020.

(b) All countries have introduced PCV by the end of 2020.

(c) At least 37 countries have introduced rotavirus vaccine by the end of 2020.

(d) At least 35 countries have introduced HPV by the end of 2020.

(e) At least 25 countries have introduced a birth dose of HepB by the end of 2020.

Objective 2: To complete the interruption of poliovirus transmission and ensure virus containment.

(a) All countries have interrupted WPV transmission by the end of 2014.

(b) All countries using OPV have introduced at least one dose of Inactivated Polio Vaccine by the end of 2015.

(c) All polioviruses are laboratory-contained and the Region certified polio-free by the end of 2018.

(d) A regional polio legacy plan is finalized by the end of 2015.

Objective 3: To eliminate measles and advocate for the elimination of rubella and congenital rubella syndrome.

(a) All countries have achieved an incidence of less than one confirmed measles case per million population by 2020.

(b) Attain MCV1 coverage ≥95% at national and district levels and at least 95% SIAs coverage in all districts.

(c) At least 25 countries have introduced rubella-containing vaccine by the end of 2020.

Objective 4: To attain and maintain elimination/control of other vaccine-preventable diseases.

(a) All countries have attained and validated the elimination of maternal and neonatal tetanus by the end of 2020.

(b) All high-risk countries have attained yellow fever immunization coverage ≥ 90% by the end of 2020.

(c) All countries within the meningitis belt have introduced MenAfriVac™ through campaigns, and 15 of them have introduced it into routine immunization by the end of 2020.

(d) Seroprevalence of HbsAg among children below five years of age is less than 2% by the end of 2020.

Guiding principles

23. The guiding principles are the following:

(a) **Country ownership** to identify and implement national immunization priorities and provide access to quality immunization for all. Countries have a responsibility for establishing good governance; communities and civil society should be actively involved and should play a pivotal role in the implementation of the immunization strategic plan.

(b) **Partnership and mutual accountability** among individuals, communities, stakeholders and governments. Experiences of global and regional collaboration in immunization will help to expand partnerships, and those at national level will be strengthened and extended to subnational level.

(c) **Access to universal health coverage** for improved health outcomes among all groups especially underserved and marginalized populations, during humanitarian emergencies, to enhance the contribution of immunization in reducing morbidity, disability and mortality from vaccine-preventable diseases.

(d) **Integration** of global disease eradication and elimination initiatives within the broader health system in close coordination with primary health care approaches. Surveillance of vaccine-preventable diseases linked to Integrated Disease Surveillance and Response as well as the use of other child health opportunities should be maximized for achieving immunization objectives.

(e) **Sustainability** through appropriate levels of financing, financial management and oversight, based on evidence-based decisions and implementation of strategies.

(f) **Innovation** and quality improvements across all aspects of immunization.

STRATEGY IMPLEMENTATION

Key approaches for implementation

24. Implementation of the **Reach Every District (RED)** approach and other locally-tailored approaches will be promoted to maximize the accessibility and utilisation of immunization services. This will ensure greater involvement of individuals and communities in moving from supply-driven to demand-driven immunization services.

25. **Extending the benefits of new vaccines to all.** Countries will be supported to introduce new vaccines and to intensify advocacy for reduction of their prices particularly for middle-income countries. Efforts should be made to improve vaccine procurement, supply and management systems while ensuring accessibility and affordability to the population in order to

achieve universal coverage. Advocacy for developing local capacity for vaccine manufacture within the African Region should continue.

26. **Sustainable immunization financing** will be pursued and domestic resources provided. Efforts to establish national budget lines and allocate and disburse funds for immunization will be supported. The need for additional resources to reach the "last fifth child" and to increase immunization coverage to at least 90% should be strongly emphasized.

27. **Integrating immunization** into national health policy and plan, with immunization interventions quantified, costed and incorporated into the various components of national health systems strengthening. Integration of additional child survival interventions with immunization should be pursued to leverage the potential for prevention of pneumonia and diarrhoea. Immunization will also be included as a priority intervention during humanitarian emergencies to save lives and reduce morbidity, disability and mortality due to vaccine-preventable diseases.

28. **Enhancing partnership for immunization.** Partnership for immunization will be expanded at country level while relying on existing regional initiatives such as Harmonization for Health in Africa (HHA). Continued use of the platform of the Interagency Coordination Committees and other national and subnational coordinating mechanisms to strengthen local partnerships and forge new ones will be strengthened.

29. **Improve monitoring and data quality**. The quality of immunization and surveillance data will be regularly monitored and its use at country level promoted. Information generated from monitoring systems and surveys will be used for advocacy and for programme and service improvement. Sensitive and high-quality surveillance including laboratory confirmation, linked to the Integrated Disease Surveillance and Response platform, should be used to monitor the epidemiological trend of vaccine-preventable diseases and guide implementation of immunization strategies.

30. **Improving human and institutional capacities.** Individual and institutional capacity to adequately plan, implement and monitor immunization programmes should be strengthened through training. The capacity to plan and manage immunization services at district and operational levels should be prioritized with a view to improving and sustaining high vaccination coverage rates.

31. **Improving vaccine safety and regulation**. Vaccine safety monitoring systems should be enhanced by strengthening the capacity of national regulatory authorities through the implementation of institutional development plans. The promotion of safe injection policies and practices and improved surveillance of adverse events following immunization should be assured. Member States' capacity to authorize and monitor vaccine clinical trials as well as compile evidence for better decision-making on new vaccine introduction should be enhanced.

32. **Promoting implementation research and innovation**. Guidance and capacity for implementation research should be strengthened. Social and anthropological studies should be emphasized for better understanding of the reasons for non-immunization of some populations and low performance of immunization programmes. Member States should be supported to implement the Algiers Declaration and the Bamako Call to Action on research for health in the African Region in order to refine strategies for improved immunization service delivery.

Roles and responsibilities

33. Governments should:

(a) Develop costed comprehensive multi-year immunization plans (cMYPs) with annual integrated operational plans.

(b) Mobilize and allocate adequate domestic resources to implement immunization plans.

(c) Enhance and sustain multisectoral collaboration and partnerships in the implementation of key approaches.

(d) Mobilize, involve and empower communities to effectively demand and utilize immunization services.

(e) Promote training, recruitment and retention of the required health workers.

(f) Conduct implementation research on the various aspects of the priority interventions.

(g) Document lessons learnt from the implementation of the past strategic plan and identify best practices for emulation and scale up.

(h) Assess the need for and, where appropriate, implement immunization during humanitarian emergencies.

(i) Coordinate the efforts and agenda of several stakeholders in line with country priorities.

34. Communities should:

(a) Promote immunization and collaborate closely with local health staff in planned fixed and outreach services.

(b) Participate in the development and testing of innovative approaches to deliver immunization services.

(c) Understand the risks and benefits of vaccination, demand safe and effective immunization programmes and participate in decision-making and service delivery processes.

(d) Empower and engage vulnerable groups, build grass-roots initiatives to track progress and hold governments and stakeholders accountable.

(e) Contribute to improved monitoring and evaluation systems.

35. WHO and partners should:

(a) Provide technical, financial and material assistance for the development of cMYPs and integrated annual operational plans.

(b) Support Member States to mobilize the necessary resources to achieve the set objectives and targets.

(c) Develop and make available updated standards and guidelines for the implementation of priority interventions.

(d) Advocate and foster continued collaboration among partners for optimal implementation of the set objectives and targets.

(e) Support countries in assessing and implementing vaccination as a priority public health intervention during humanitarian emergencies.

(f) Document and disseminate best practices of countries.

RESOURCE IMPLICATIONS

36. Implementation of the Regional Strategic Plan for Immunization 2014–2020 will require a high level of national and international commitment. Financial support is required for full implementation of comprehensive national immunization plans in order to achieve the set objectives and targets. Improving immunization services should be integrated into the overall health system strengthening.

37. Provisional estimates[20] show that the total annual financial requirement for immunization in the Region was US$ 1.8 billion in 2013. It is estimated that governments and partners financed, respectively, a little over 30% and 50% of the financial requirements, leaving a funding gap of approximately US$ 340 million.

38. Over the period of 2014–2020, based on the projections of targets, the provisional total cost for the Region is estimated at US$ 17.2 billion. In order to achieve the targets as articulated in the Regional Strategic Plan for Immunization, financial requirements would have to increase annually, reaching an estimated total of US$ 2.8 billion by the end of 2020. This increase represents additional resources of US$ 4.2 billion required for 2014–2020.

39. Based on historical patterns and trends of financing by Member States and partners, a persistent regional funding gap of 20% to 22% per annum should be anticipated over the timeframe of 2014–2020. Member States and partners are therefore encouraged to mobilize the additional resources required to adequately finance national immunization plans that have provisions for procurement of vaccines, strengthening of human resources, conduct of surveillance, programme management, and improvement of supply chain performance.

MONITORING AND EVALUATION

40. Immunization monitoring indicators recommended by the GVAP should be adapted to the regional context and used to monitor the implementation of this plan annually. Standardized programme evaluation instruments, including appropriate indicators, should be revised and updated to reflect current priorities. A mid-term programme evaluation should be conducted in 2017 and a comprehensive end-term evaluation of the strategy should be conducted in 2020.

41. The Task Force on Immunization in Africa should conduct annual assessment of the progress towards the achievement of the objectives and targets of the Regional Immunization Strategic Plan 2014–2020. The results should be used to re-align and refine the implementation of the regional plan. A progress report should be presented every year to the Regional Committee.

ASSUMPTIONS AND RISKS

42. Optimal implementation of the Regional Immunization Strategic Plan 2014–2020 will depend on government stability and absence from human-made emergencies that facilitate good

[20] Provisional estimates are extracted from the on-going Decade of Vaccine Costing, Financing and Funding Gap Analysis and based on the comprehensive Multi-Year Plans (cMYP) of 39 countries of the African region (high and upper middle income countries, except Angola, are not included in the analysis).

governance and leadership, leading to increased national commitment to sustain immunization services.

43. Climate change will not significantly change the geographical patterns of the burden of vaccine-preventable diseases and major break-downs in vaccine supply will be mitigated by multiple vaccine manufacturers able to deliver vaccines to countries in a timely fashion.

44. The private sector has adequate incentives to provide immunization services or related expertise in logistics or research.

CONCLUSION

45. The implementation of the Regional Immunization Strategic Plan 2014–2020 will build on the experiences from the past in a manner that strengthens immunization systems. It should also inspire the development of a comprehensive multi-year and operational country plans.

46. The strategic thrusts are to build the competences of health workers to plan, implement and monitor immunization services and strengthen the cold chain system and vaccine management practices. Implementation research will be required for enhanced understanding and better implementation of key approaches to improve and maintain high level vaccination coverage.

47. The implementation of the Regional Immunization Strategic Plan will require country ownership supported by a committed global and regional partnership as well as broad-based local partnerships in order to ensure the availability and efficient use of resources.

48. The Regional Committee is invited to examine and adopt the actions proposed.

TFI Members Meeting, Brazzaville, Congo
04-05 December 2014
Draft Recommendations

General considerations

- The TFI acknowledged that the current Ebola crisis has devastated communities and health services in the three most affected countries, and recognised the importance of the role of the WHO regional office in the response to the outbreaks. The TFI also recognised that the diversion of the Secretariat to work on the Ebola response was essential but that it had inevitably affected some immunisation activities. The TFI wishes to express its strong words of support to all national and external health staff engaged in the response to the Ebola outbreaks in affected countries and congratulate the WHO Regional Office for its current contribution to this effort. Finally, the TFI was encouraged by the speed of development of the various candidate Ebola vaccines.

- The TFI discussed the need to revitalize the working groups established in previous year and ensure that the Chairs of these working groups, with the assistance of the members of the WHO Secretariat, set up meetings or conference calls with working group members in the first quarter of 2015. The Data Quality and Use working group had met and gave an interim report. Highlights of this included: what tools are required; barriers to the collection of quality data including falsification because of incentivisation, fear of entering accurate data in case this is prejudicial to HCWs, importance of HCWs understanding what data is required for; how to align activities with GAVI; etc. A full report of the Data Quality and Use Working Group will be made available at the June 2015 TFI meeting.

- The structure of future TFI meetings was extensively discussed and the Members agreed on the principle of having future meetings held twice a year in June and December. Proposed dates for the next two years will be suggested very soon for TFI Members deliberation and to ensure that dates are set in diaries with good notice.

- The TFI noted that countries are receiving many recommendations for action from SAGE, TFI, GAVI, etc. The challenge is how the regional office can offer more support to countries as they consider these recommendations, prioritise them and implement them.

- The TFI also acknowledged the useful contribution of the Independent Monitoring Board (IMB) to the achievement of polio eradication. TFI discussed the IMB recommendation that the WHO HQ take over the management of the Central African outbreak from the African Regional office, and expresses strong reservation about the suggestion as this fundamentally changes the mandate of HQ and regional offices which have the responsibility of working with countries.

- TFI commended the Regional Director and Member States delegates to the 2014 Regional Committee Meeting (RC64) for their adoption of the draft Regional Strategic Plan for Immunization 2014-2020 and noted with satisfaction their valuable contribution to further improve the document.

- The additional following considerations were also agreed upon by the TFI:

- The duration of future TFI meetings should be extended to three days and should also include the participation of representatives of different clusters within WHO/AFRO (e.g. Health Systems Strengthening, Disease Prevention and Control, Health Promotion, etc.) as well as representatives of major immunization donors/partners in the Region as observers. The first day of future meetings will be devoted to the TFI working groups' discussions as appropriate.

- There will be two conference phone calls prior to each TFI meeting. Each call will have preparatory discussions about agenda items with pre-reading materials where possible.

- Key documents pertinent to each topic on the agenda should be shared with TFI Members at least 5 working days prior to the TFI meeting. The number of slides in each presentation should be limited to a strict minimum to avoid information overload and allow ample discussion on the topics put forward to TFI Members. A copy of slides relevant to the topic of each presentation should be included in the binder given to TFI Members. The specific input from TFI on each item presented should be displayed at the end of each presentation. This invited input should be appropriately supported by the extent and depth of the information presented to the TFI.

- In addition, it was agreed that the June 2015 TFI meeting should include agenda items to allow for an extensive discussion on the progress towards measles elimination and rubella vaccine introduction in the Region.

- A major focus of the TFI's work will be to monitor the implementation of the Regional Strategic Plan for immunization 2014-2020 and this will be a standing agenda item for all TFI meetings. The agenda of each meeting will be determined by TFI for the next two years allowing for addition of topical issues.

- TFI should have an in-depth review of progress against the GVAP goals and targets once per year. It was agreed that the best time to do this will be during a meeting held in June when country reports will be available for the previous year, and when the TFI report can be used to inform the subsequent SAGE GVAP working group discussions.

- At the June meeting, there should be enough time devoted to extensively review the available data in order to meaningfully assess the progress towards GVAP set goals and objectives in the African Region.

Recommendations on Polio Eradication in the African Region

No	Recommendations/Follow-Up Actions	Responsible	Deadline
1.	In order to support countries in the process of polio certification and containment, WHO/AFRO and the partners should undertake more advocacy activities to get countries committed to develop risk mitigation strategies as this is important to both polio eradication initiative and routine immunization strengthening.	WHO/AFRO	Ongoing

No	Recommendations/Follow-Up Actions	Responsible	Deadline
2.	Considering the weak surveillance system as well as the suboptimal implementation of the response activities to the WPV outbreak in Equatorial Guinea, WHO/AFRO and Partners should undertake high level advocacy mission to Equatorial Guinea.	WHO/AFRO	Next TFI Meeting
3.	While AFP surveillance and overall coverage of SIAs have improved in Cameroon, quality is uneven with remaining gaps in detection and timely investigation of cases. A number of districts are still missing a large number of children in SIAs. Government of Cameroon is strongly encouraged to fully implement the recommendations of the Central Africa TAG meeting and other advocacy visits to ensure accountability of underperforming districts, enhance commitment and ownership of regional and national authorities.	WHO/AFRO	Ongoing
4.	The Central African Republic remains at a very high risk of an outbreak of polio. The program should put in place sufficient technical, logistic, operational capacity to support the government and engage all NGOs in implementing key risk mitigation strategies, particularly improving AFP surveillance, high quality immunization campaigns, and ensuring coverage of displaced and border populations.	WHO/AFRO	Ongoing
5.	TFI noted that many national immunisation programmes are dependent on polio infrastructure and funding to support other routine services, including most recently being used in response to the Ebola Virus Disease outbreak, and that there is a serious threat to these services once the polio eradication funding is withdrawn. Furthermore, there are best practice and lessons to be learnt from the PEI, and these need to be identified for application to routine immunisation services. The TFI working Group on Country Ownership is asked to review planning for the Polio Legacy, for which little progress had been made, as a priority question and provide a report to TFI in the December meeting. With regard to the development of a regional polio legacy plan as stipulated in the Regional Strategic Plan for Immunization 2014-2020: o Advocacy related to the management of Polio assets and infrastructure should be anchored on multifaceted ventures like the GVAP or the health systems strengthening broader agenda to encourage sustained support for implementation of national immunization programs. o Adequate communication strategy should be developed during the period of the legacy planning. o The TFI working group on country ownership should play a critical role in moving the polio legacy plan forward.	WHO/AFRO	Ongoing

No	Recommendations/Follow-Up Actions	Responsible	Deadline
6.	In order to optimally support countries in the introduction of the IPV vaccine and prepare for "the switch" between the tOPV to bOPV vaccines, WHO/AFRO should o Develop a risk management strategy for "the switch" in the African Region which includes at least one back-up strategy in case the planned scenarios are not met. The strategy should be simpler for easier understanding and higher likelihood of distinguishing preconditions, milestones and steps that are essential from others that are less critical to a successful "switch". o Rehearsals for "the switch" must be built into the timeline of the process and this should include pilots of this switch in a limited number of countries.	WHO/AFRO	Next TFI meeting

Recommendations on Ebola Virus Disease (EVD) Outbreak in West Africa and its Impact on Immunization systems

No	Recommendations/Follow-Up Actions	Responsible	Deadline
1.	Considering the negative impact the EVD outbreak has had on immunization systems in the most affected countries in West Africa, a TFI working group on Ebola should be established with the mandate of recommending the best ways of restoring immunisation services in the affected countries.	WHO/AFRO	Next TFI Meeting
2.	The spread of polio to an Ebola-affected country could be devastating and would be a major setback for polio eradication in the region. Recognising that historically, polio spread in West Africa is overland through known migratory pathways and populations, special risk mitigation efforts should be made in countries and districts surrounding the Ebola-affected countries to improve population immunity to polio and enhance sensitivity of poliovirus surveillance.	WHO/AFRO	Next TFI Meeting

Recommendations on GVAP & Regional Strategic Plan for Immunization 2014-2020

No	Recommendations/Follow-Up Actions	Responsible	Deadline
1.	Countries with the support of WHO/AFRO and partners should put in place specific mechanisms to ensure that civil society organizations are fully involved in the activities aimed at addressing vaccine hesitancy/confidence in the Region.	WHO/AFRO	Ongoing
2.	In line with the endorsement of the Regional Strategic Plan for Immunization 2014-2020 by RC64 in November 2014: o WHO/AFRO and partners to use the opportunity of the next EPI Managers meetings to discuss the development and implementation of costed national immunization multi-year plans in line with the Regional strategy.	WHO/AFRO	Ongoing

	○ WHO/AFRO should provide relevant tools for monitoring and evaluation of the implementation of the costed national immunization plans. ○ WHO/AFRO and partners to support countries in setting up appropriate independent structures for the monitoring of the objectives and targets of their national plans.		

Recommendations on Implementation Research Guide for EPI Managers

No	Recommendations/Follow-Up Actions	Responsible	Deadline
1.	The Implementation Research guide for EPI Managers in the African region was reviewed and endorsed by the TFI. The following amendments were suggested by TFI before its wide dissemination: ○ WHO/AFRO to incorporate feedback received from TFI members. ○ The implementation research guide should be presented to EPI managers during their next year meetings. ○ WHO/AFRO to publish and disseminate widely the guide to implementation research to all stakeholders.	WHO/AFRO	Ongoing

Summary report on the

Twenty-eighth meeting of national managers of the Expanded Programme on Immunization

WHO-EM/EPI/342/E

Amman, Jordan
16–19 November 2014

World Health Organization
Regional Office for the Eastern Mediterranean

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Summary report on the

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Contents

1. Introduction

The Twenty-eighth meeting of national programme managers of the Expanded Programme on Immunization (EPI) was organized by the WHO Regional Office for the Eastern Mediterranean in Amman, Jordan, from 16 to 19 November 2014. The meeting was part of a series of meetings, which included a meeting of chairpersons of National Immunization Technical Advisory Groups (NITAGs) on 20 November 2014, a meeting of national measles/rubella laboratories focal points on 21 November 2014, and the fifteenth intercountry meeting on measles/rubella control and elimination from 22 to 25 November, 2014.

The objectives of the meeting were to:

- review national and regional progress in EPI: achievements, constraints and the way forward in view of the Global Vaccine Action Plan (GVAP);
- discuss recent advances in new vaccines and technologies: progress, constraints and the challenges facing their use;
- update Regional Technical Advisory Group (RTAG) members on progress and constraints facing EPI and get RTAG input for supporting EPI.

The meeting was attended by national EPI managers from countries of the Eastern Mediterranean Region, chairpersons of NITAGs and the RTAG, representatives from the United Nations Children's Fund (UNICEF) headquarters, regional offices and country offices, the Centers for Disease Control and Prevention (CDC, Atlanta), Sabin Vaccine Institute, Network for Education and Support in Immunization (NESI), Agence de Médecine Préventive (AMP), and

WHO staff from headquarters, the Regional Office and country offices.

The meeting was inaugurated by Dr Ala Alwan, WHO Regional Director for the Eastern Mediterranean. Dr Alwan reiterated the importance of achieving high coverage with routine immunization and the addition of new vaccines to immunization schedules, as appropriate, and in line with WHO recommendations to achieve the targets of the Millennium Development Goals. He highlighted the need for scale up efforts to achieve eradication of poliomyelitis. While commending the achievements of immunization programmes in many countries, Dr Alwan cautioned that much still remained to be done in order to achieve regional and global targets. He thanked partners for their support and said that innovative ways were needed to overcome prevailing challenges faced by the EPI in various countries and to ensure effective use of available resources.

The 4-day meeting comprised five sessions which included global and regional briefings on: the need to strengthen routine immunization in countries of the Region to meet EPI targets; the poliomyelitis eradication initiative (PEI), including objective 2 of the Polio Eradication and Endgame Strategic Plan 2013–2018; and the hepatitis B control target. The meeting included groupwork on enhancing implementation of objective 2 of the Polio Eradication and Endgame Strategic Plan and reviewing country situations of hepatitis B control and outline plan for implementation of required activities.

Dr Musaab Alsaleh (Kuwait) chaired the meeting.

2. Summary of discussions

Participants noted the slight drop in reported DTP3 coverage in the Region despite substantial constraints and challenges that several countries have experienced – and expressed appreciation to the EPI in Egypt, Tunisia, Libya and Yemen for the extra efforts devoted to maintaining the high performance of the programme.

They also noted the 6% increase in penta3 coverage in Yemen in 2013, compared to 2012.

They expressed appreciation that the EPI would be a regular agenda item at each session of the Regional Committee for the Eastern Mediterranean.

The regional achievement of the introduction of Hib vaccine in all countries of the Region and progress in introducing other new vaccines was commended.

Remarkable improvements in provision of routine immunization to Syrian refugees in countries neighbouring Syria was acknowledged, in addition to the efforts and collaboration of host countries and partners, as well as the solidarity of countries in the Region.

Participants noted the comments of the polio oversight body on the excellent response to ongoing wild poliovirus transmission in the Region but noted with concern the ongoing transmission in Pakistan and Afghanistan, which was posing a threat to the entire Region, and the negative impact it had had on the EPI programme in these countries, in which the number of polio national immunization days had been very high.

Participants acknowledged that regional EPI-related targets (polio eradication, measles elimination, etc.) would not be met by the target date of 2015 and underlined the need to accelerate efforts to meet regional and national targets for the eradication, elimination and control of vaccine-preventable diseases.

It was agreed that it was important to accelerate implementation of recommendations of previous EPI managers' meetings.

3. Recommendations

Strengthening routine immunization

1. Countries that have not yet achieved routine immunization coverage targets (at least 90% DPT3-containing vaccine coverage at national level and 80% in all districts) should:
   - 1.1 Pay more attention to analysing district-level data and identifying unreached populations and the barriers to immunization and apply appropriate strategies to reach the unreached.
   - 1.2 Develop and implement appropriate communication and social mobilization strategies to raise community awareness, address cultural barriers and increase and maintain the highest level of demand for immunization. Countries should expand social mobilization activities, implemented in relation to polio eradication activities, to increase awareness of routine immunization. Countries are encouraged to document best practices related to implementation of communication and social mobilization strategies.

2. Countries with well-performing EPIs should pay enough attention to sustaining the achievements of the programmes, ensuring high quality of all components of the immunization system and bridging any gaps in view of the multiple priorities of the programme.
3. The Regional Office should use all opportunities, including sessions of the Regional Committee, to advocate, at the highest levels, for raising the visibility of regional immunization targets and sustaining government commitment towards scaling up immunization programmes in all countries, including the better performing countries, in order to achieve immunization targets.
4. In line with the Global Vaccine Action Plan (GVAP), endorsed by the World Health Assembly in May 2012:
   4.1 The Regional Office should conduct necessary advocacy and awareness strengthening activities (including Regional Committee resolutions) to secure the required regional and country support to ensure adequate implementation of the GVAP.
   4.2 All countries should revise their EPI multi-year plan and related strategies to be in line with the GVAP, and should report annually to the Regional Committee on implementation of the GVAP at the national level.
5. Considering the recent SAGE conclusion concerning use of acellular pertussis (aP)-containing vaccine, stating in particular that: licensed aP vaccines have lower initial efficacy, faster waning of immunity, and possibly a reduced impact on transmission of pertussis , as compared to currently internationally available whole cell pertussis (wP)-containing vaccines, and are less effective in clearing mucosal infections than wP vaccines, as indicated by the fact that four out of the five countries where resurgence of pertussis has occurred were exclusively using aP

vaccines, and the recent modelling studies from Australia, England and Wales, and the United States of America, as well as data from a baboon model, that supported the hypothesis that transition from wP to aP vaccine may be associated with disease resurgence; participants recommended the following:

5.1 Countries that are using wP-containing vaccines should continue to do so and should not switch to aP-containing vaccines for the primary series of immunization (initial 3 doses of the infant immunization).

5.2 Countries that have introduced aP-containing vaccine in the primary series of immunization, should institute laboratory-based pertussis surveillance and take necessary measures if resurgence of pertussis occurs. The NITAG in these countries should review all available information in order to decide about continuation/discontinuation of aP vaccination of the primary series of immunization.

6. In view of the stretched health systems in countries hosting Syrian refugees, WHO and partners are requested to mobilize more resources to enable these countries to continue regularly providing routine immunization to Syrian refugees. Partners, especially the GAVI Alliance, are requested to support these countries in gaining access to procurement of vaccines at affordable prices.
7. WHO, UNICEF and other partners, in collaboration with the host country, are requested to support documentation of the strategies, best practices and lessons learnt concerning implementation of immunization activities in Syria and the countries hosting Syrian refugees.
8. WHO and partners are to support collaboration and coordination of implementation of cross-border immunization and surveillance activities in all countries in need.

Implementation of objective 2 of the Polio Eradication and Endgame Strategic Plan

9. In terms of strengthening routine immunization using global PEI assets countries of the polio Endgame Strategic Plan (Afghanistan, Pakistan and Somalia) are urged to accelerate implementation of the EPI/PEI synergy plan for strengthening routine immunization in respective countries and report quarterly to the Immunization System Management Group, through the Regional Office, on progress of implementation.
   9.1 As envisaged under objective 2 of the Endgame Strategic Plan, PEI staff in WHO and UNICEF should dedicate a significant amount of time to strengthening routine immunization in coordination with the respective EPI units.
   9.2 In view of ongoing wild poliovirus transmission and while taking the national EPI onboard, PEI team leads of WHO and UNICEF are encouraged to review the current EPI/PEI synergy plan for strengthening routine immunization so as to establish a realistic timeframe for its implementation, monitoring and accountability.

Introduction of inactivated poliovirus (IPV)

10. In order to ensure maximum immunogenicity to IPV, at least one dose of the vaccine should be administered at 14 weeks of age or soon after, as an additional dose to the ongoing oral poliovirus schedule, as per WHO recommendations.
   10.1 Djibouti is urged to take the necessary action for submitting GAVI application for introduction of IPV vaccine by GAVI's deadline of 25 January 2015.

10.2 All countries that have not introduced IPV vaccine should accelerate the registration of prequalified vaccines to avoid any delay in the planned introduction date. Countries are encouraged to register all available prequalified IPV vaccines in order to ensure availability of alternate sources of the vaccine in case of shortage of the vaccine produced by any manufacturer.

10.3 WHO and UNICEF are requested to encourage vaccine producers to submit their files for IPV registration in the different countries as soon as possible.

10.4 WHO is requested to support countries to implement fast track registration of IPV vaccine.

tOPV-bOPV switch

11. All countries are encouraged to register all available prequalified bOPV vaccines, for use in routine immunization (as soon as the products are prequalified by WHO for use in routine immunization), in order to ensure availability of alternate sources of vaccine supply in case of shortage.

11.1 WHO and partners are requested to accelerate the finalization of the operational protocol, including the readiness assessment tool, for implementation of tOPV-bOPV switch.

11.2 All countries are required to consider developing national plans of action for implementation of the switch in line with WHO-related guidance.

11.3 GPEI is to mobilize necessary resources for supporting the operational cost of the switch in low resource countries, including replacement/compensation of destroyed tOPV stocks.

11.4 WHO and UNICEF are requested to encourage vaccine producers to submit their files for registration of bOPV in the different countries, where possible.

11.5 WHO is requested to support countries in the implementation of fast track registration of bOPV vaccine.

11.6 WHO and UNICEF are requested to initiate a system for mapping vaccine procurement and vaccine stock of the self-procuring countries in order to help the countries keep minimum stock of tOPV at the time of the switch and procure bOPV in a timely manner.

11.7 WHO is requested to send a letter from the highest level of WHO and UNICEF to all countries informing of the tOPV-bOPV switch long in advance of the official switch date, in order for countries to initiate preparation in good time.

Hepatitis B disease reduction target

12. All countries that have not yet introduced hepatitis B birth dose should make all efforts to introduce it.

12.1 Countries that have not introduced hepatitis B birth dose due to financial problems, should make every effort to secure necessary resources from domestic resources or through partners' support. Those countries should identify the target and strategies of implementation and develop national plans for introduction of hepatitis B birth dose and use these plans for advocacy and resource mobilization.

12.2 GAVI Alliance partners and representatives of the regional constituency in the GAVI Board are to explore the possibility of GAVI support to introduction of birth dose in GAVI-eligible countries.

12.3 Countries that have not introduced hepatitis B birth dose due to low institutional delivery rate are requested to introduce the birth dose even if the expected coverage figures are not high in the beginning, and should develop a plan of action for phased expansion of hepatitis B birth dose.

13. All countries are to make every effort to increase the coverage with the birth dose delivered within 24 hours of birth.

13.1 Countries should formulate necessary policy and legislation to ensure administration of birth dose of hepatitis B vaccine in all maternity care institutions, public and private.

13.2 National EPI programmes should coordinate with maternal and child health and other related departments and stakeholders (private sector, professional associations) and concerned partners to improve delivery of the birth dose within the first 24 hours of life.

13.3 Countries in which a large proportion of deliveries are occurring outside health care institutions should identify innovative approaches and locally suitable solutions (e. g. using lady health workers), as well as using new technologies (uniject) for administration of the birth dose.

13.4 WHO and partners are to expedite availability of prequalified hepatitis B uniject at affordable cost, for use in selective settings outside health care institutions.

14. All countries, that have not recently done so, are encouraged to conduct hepatitis B sero-prevalence survey, using the WHO guidelines "Documenting the impact of hepatitis B immunization: best practice for conducting a serosurvey",[1] to document the

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[1] World Health Organization Department of Immunization, Vaccines and Biologicals. Documenting the impact of hepatitis B immunization: Best

impact of the hepatitis B vaccination programme and progress towards achieving the 2015 regional hepatitis B disease reduction target and/or use the data for further advocacy for introduction/improving coverage of the birth dose.

15. Countries that are ready for verifying achievement of the control target should identify an independent national body of experts with key technical expertise, including EPI experts, epidemiologists, virologists, clinicians/paediatricians and public health physicians, for verification of achieving the hepatitis B control target and submission of the country's verification report to the Regional Verification Commission. Where possible, countries are encouraged to utilize existing suitable national committees, with necessary modification, for verification activities of hepatitis B control target.
16. WHO and partners are to provide necessary technical support to countries, if requested, for undertaking hepatitis B sero-surveys.
17. WHO should finalize guidelines for verification of achievement of the hepatitis B control target in the Eastern Mediterranean Region and make these guidelines available to countries by January 2015.

Improving monitoring and evaluation of EPI

18. In order to utilize the opportunity of upcoming demographic and health/multiple indicator cluster surveys and to ensure high quality of the results related to EPI, the EPI programme should proactively collaborate and coordinate with the responsible entity for conducting these surveys to ensure that recording practices are well understood by surveyors and the needs of EPI programme are

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practices for conducting a serosurvey. Geneva: World Health Organization; 2011. Report No. WHO/IVB/11.08.

adequately addressed. EPI programmes are encouraged to improve proper use and retention of home-based records (vaccination cards) as, among other purposes, they serve as primary documentation for coverage surveys.

19. WHO and partners are to provide necessary technical support to countries in order to identify appropriate ways for estimating the denominator of calculating the administrative vaccination coverage.
20. WHO is requested to resolve, with the GAVI Alliance, the interpretation of the country official estimates (sheet 5 of the joint reporting form), that allow for providing only vaccination coverage without providing the number of vaccinated children.

Improving vaccine management and logistics

21. All countries, that have not yet done so, are encouraged to conduct assessment of the effective vaccine management system, develop an improvement plan and allocate/mobilize necessary resources for its implementation.
22. All countries should strengthen their immunization supply chain system, invest in human resources capacity-building and develop continuous improvement plans for their immunization supply chains, using the latest available technologies and state-of-the-art practices.
23. All countries should appoint a properly trained immunization supply chain manager and ensure proper management of the supply chain from the demand and vaccine forecasting phase until delivery to the end-user.

24. WHO and UNICEF are to provide the necessary technical support for implementation of effective vaccine management upon countries' request.

Planning and financing for immunization

25. All countries are encouraged to develop comprehensive multi-year plans and annual workplan for immunization as per WHO/UNICEF guidelines and in line with the GVAP and allocate/mobilize necessary resources for its implementation.
26. Countries to pay special attention for accuracy of reporting of joint reporting form financing indicators.
27. WHO to adjust joint reporting form reporting to accommodate financial information reporting from Member States with different fiscal and calendar years.

Summary report on the

Fifteenth intercountry meeting on measles/rubella control and elimination

WHO-EM/EPI/343/E

Amman, Jordan
22–25 November 2014

World Health Organization
Regional Office for the Eastern Mediterranean

WHO-EM/EPI/343/E

Summary report on the

Fifteenth intercountry meeting on measles/rubella control and elimination

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Document WHO-EM/EPI/343/E/01.15

Contents

1. Introduction

The WHO Regional Office of the Eastern Mediterranean organized the fifteenth intercountry meeting on measles and rubella control and elimination in Amman, Jordan on 22–25 November, 2014. The meeting was part of series of back-to-back related meetings which also included the 28th intercountry meeting of national managers of the Expanded Programme on Immunization (16–19 November 2014), meeting of Chairpersons of National Immunization Technical Advisory Groups (NITAGs) of countries of the Eastern Mediterranean Region (20 November 2014) and meeting of the focal points on the national measles/rubella laboratories in countries of the Region (21 November 2014).

The objectives of the meeting were to review country progress towards achieving the regional measles elimination target, follow up on implementation of the different components of regional strategy for measles elimination and review and update the national plans for strengthening measles/rubella elimination and control programmes.

The meeting was attended by delegates from all countries of the Region, WHO immunization and polio-related staff from country, regional and headquarters level, as well as by representatives of different partners including the Centers for Disease Control and Prevention (CDC Atlanta), GAVI Alliance and UNICEF.

The meeting was inaugurated by Dr Ezzeddine Mohsni, Acting Director, Communicable Disease Prevention and Control, WHO Regional Office for the Eastern Mediterranean. Dr Rana Safdar (Pakistan) chaired the meeting.

The meeting entailed three main sessions: the global and regional situation; progress in achieving and sustaining population immunity against measles and rubella; and progress in achieving the target of

measles/rubella surveillance performance indicators. Two break-out group work sessions were dedicated to discussing in detail country situations with regard to achieving the required population immunity and its impact on measles/rubella occurrence, as well as the situation of measles rubella surveillance. The group work discussion dedicated time for following up on implementation of the planned activities in 2013–2014 and discussing the planned activities for 2014–2015. A third group work session was dedicated to drafting national plans for activities related to strengthening all aspects of EPI, including the technical support required for implementation of the planned activities.

The countries and the partners expressed their appreciation for the level of the technical discussion, the input, active participation and transparency in sharing information by the delegates from all countries

2. Conclusions

Participants discussed the reduction in the total number of measles cases in 2014 compared to the same period of 2013. They noted the progress made by several countries of the Region and commended the continuous achievement of Bahrain, Oman and Palestine, that have reported no endemic measles virus transmission for three years or more, and the Islamic Republic of Iran, Morocco and Tunisia, which had very low measles incidence in 2013–2014. The participants commended also the action taken by Jordan and Lebanon to control measles outbreaks in 2013 and the subsequent reduction in measles incidence in the two countries in 2014.

Concern was expressed about the significant increase in the number of measles cases in Egypt and Iraq over the past two years. As well, a large number of measles cases occurred in Sudan in 2014, despite the high reported administrative coverage of the measles supplementary immunization activities that were implemented late 2013. Concern was

also raised about the large number of measles cases in several countries reporting high coverage with 2 doses of routine measles vaccine and/or high coverage of recent supplementary immunization activities, including Kuwait, Qatar and the United Arab Emirates.

Participants concluded that there is a high likelihood that the regional target for measles elimination by 2015 will not be achieved in most countries and they underlined the need for accelerating efforts to achieve the target.

The meeting reiterated the validity of recommendations of previous meetings and issued a number of additional recommendations.

3. Recommendations

To all countries

1. Countries are strongly urged to strengthening routine vaccination services to achieve high coverage with the 2 doses of measles vaccines at the district level. Countries should follow up the MCV1/MCV2 drop-out rate and implement appropriate measures to minimize the drop-out, including raising population awareness and defaulter tracing.
2. Countries undertaking supplementary immunization activities should ensure high quality activities through proper planning, optimum implementation, monitoring and supervision. Countries are also urged to conduct post-activity coverage evaluation surveys and implement mop-up activities where needed.
3. Countries reporting high coverage of routine measles vaccination, including those with low reported measles incidence and those experiencing frequent outbreaks/high endemicity, should consider validating the measles vaccination coverage data through conducting

data quality self-assessment (DQS) and/or vaccination coverage evaluation surveys periodically.

4. All countries are urged to strengthen measles case based laboratory surveillance and achieve the required measles surveillance performance indicators at the district level
5. In view of the current constrained global supply, especially for MMR vaccines, countries should exercise long-, mid- and short-term forecasting to guide the vaccine industry in planning production of appropriate vaccines. In order to avoid supply shortages, countries should ensure timely contracting and procurement of vaccines and other immunization supplies.
6. If procurement is to take place through UNICEF, countries should ensure advance planning of vaccine procurement. On average, 8–12 weeks needs to be allowed for delivery of vaccines from the time of release of funds until arrival in the country. For large-scale campaigns that require significant quantities of vaccine, longer lead times may apply.
7. All countries to move to weekly reporting of measles/rubella case based surveillance data to the WHO Regional Office and to ensure timely reporting of measles/rubella outbreaks.
8. Countries are urged to strengthening human resource capacity to respond to the requirements for measles elimination activities.
9. All countries are to report to the next meeting on action taken on implementation of recommendations of the meeting.

To WHO and partners

10. Provide necessary technical support to the countries for:
    - planning, implementation, monitoring and evaluation of supplementary immunization activities
    - strengthening case-based laboratory surveillance of measles and rubella
    - verifying elimination of measles in the relevant countries.

11. Conduct a regional training workshop on measles elimination verification procedures for countries close to verifying elimination.
12. Support Egypt, Iraq and the Syrian Arab Republic to expedite registration of available WHO prequalified measles-containing vaccines.

To specific countries

Afghanistan

- Improve routine vaccination coverage of MCV and monitor the Penta1-MCV1 and MCV1-MCV2 dropout rates and implement appropriate measures to minimize drop out, including proper implementation of the RED approach, raising population awareness and defaulter tracing.
- Ensure proper planning and implementation of the measles supplementary immunization activities planned for 2015 and supported by GAVI, using appropriate readiness assessment dashboard to ensure adequate preparation.
- To address the low measles surveillance performance indicators, strengthen measles/rubella case-based surveillance through extensive training of health workers on measles/rubella surveillance and case investigation and raising awareness among all health professionals on the importance of reporting all fever/rash suspected cases.

Bahrain

- In light of the recent 3-cluster outbreaks of measles in an under-vaccinated special population/high-risk community, and occurrence of hospital transmission of the disease:
  - strengthen routine immunization and ensure adequate screening for vaccination status on pre-school and school entry;
  - review hospital infection control practices and health-care worker vaccination policy and apply corrective measures as needed.

- In light of the occurrence of a relatively large number of rubella cases among Bahraini and non-Bahraini aged < 5 years, consider reviewing the vaccination schedule to implement the second dose of MMR during the second year of age instead of the current schedule at school entry and use school entry as an opportunity for checking vaccination status.
- In view of the high routine vaccination coverage in Bahrain and the possibility of false positive cases of rubella due to cross reactions, where there are rubella IgM positive cases without supportive epidemiologic evidence, consider reviewing rubella case investigation procedures and introducing additional diagnostic evaluations (e.g. testing for parvovirus B19 and other pathogens).

Djibouti

- Strengthen routine vaccination services, through implementation of the RED approach, to achieve high coverage with the 2 doses of measles vaccines at the district level.
- Follow up the MCV1/MCV2 drop-out rate and implement appropriate measures to minimize the dropout rate, including raising population awareness and defaulter tracing.
- Conduct a measles follow-up campaign in 2015 to cover population immunity gaps resulting from relatively low coverage of MCV1 and MCV 2 and the fact that the last measles follow-up campaign was done in 2012.
- Establish measles/rubella case based laboratory surveillance, utilizing the available support from the Regional Office and other partners.

Egypt

- In view of the rapidly increasing incidence of measles along the past 2 years, especially among the younger age group, and the shortage of MCV that Egypt is facing, Egypt should:
  - Ensure regular availability of measles-containing vaccine and expediting registration of available WHO prequalified vaccines

  - Restore the strength of routine immunization activities and implement outreach activities in the low coverage districts.
  - Develop and implement communication and social mobilization strategy to improve population demand to vaccination, especially in the slum areas
  - Implement a nationwide follow-up campaign, using MR or MMR vaccine (if available) targeting appropriate age group, based on disease epidemiology.
- In view of the under reporting of measles cases, Egypt should strengthen measles/rubella case-based surveillance through:
  - Extensive training of health workers on measles/rubella surveillance and case investigation
  - Raising awareness among all health professionals on the importance of reporting all fever/rash suspected cases
  - Instituting specimen collection in all health facilities receiving suspected cases (not only in the hospitals) through appropriate training and supply of specimen collection kits.

Islamic Republic of Iran

- Consolidate elimination activities in order to achieve interruption of endemic transmission of measles by 2015.
- Prepare for documentation for measles elimination verification. The National Verification Committee should meet regularly to guide the country towards completing elimination activities.

Iraq

- In view of the decreasing routine vaccination coverage along the past 6 years and in view of the rapidly increasing incidence of measles, especially among the younger age group during the past 2 years, and in view of the current vaccine shortage, Iraq should:
  - Ensure regular availability of measles-containing vaccine and expedite registration of available WHO prequalified vaccines

- Strengthen routine vaccination services to achieve high coverage with the 2 doses of measles-containing vaccines at the district level
- Follow up the MCV1/MCV2 dropout rate and implement appropriate measures to minimize drop out, including raising population awareness and tracing defaulters
- Implement a nationwide follow up campaign, using MR vaccine, targeting appropriate age group based on disease epidemiology.

Jordan

- Despite the significant reduction in measles cases in 2014 compared to 2013, Jordan needs to exert additional efforts to restore the status of interruption of endemic measles virus transmission through strengthening routine immunization and conducting targeted supplementary immunization activities.
- In view of the low measles surveillance performance indicators, especially the reporting rate, Jordan should strengthen measles/rubella case-based surveillance through extensive training of health workers on measles/rubella surveillance and case investigation and raising awareness among all health professionals on the importance of reporting all fever/rash suspected cases.
- Improve the functionality of the expert committee and consider replacing inactive members to ensure regular meetings of the committee.

Kuwait, Qatar, Saudi Arabia and United Arab Emirates

In view of the continued outbreaks of measles, despite the high reported routine vaccination coverage with 2 doses of MCV and the several supplementary immunization activities conducted in each country, and in view of the relatively common epidemiological and social situation and geographical proximity of the 4 countries, the following actions are recommended.

- Strengthening routine immunization

  - Review the routine immunization policy and review the routine immunization schedule to provide the second dose of measles-containing vaccine during the second year of life in order to prevent accumulation of susceptible children, and check completeness of the vaccination schedule at school entry.
- Conducting timely and synchronized MR/MMR campaigns targeting a wide age-range population
  - Target age group should be based on the epidemiology of measles and rubella in each country.
  - Ensure high quality supplementary immunization activities through proper timely planning, adequate district microplanning, and optimum implementation, monitoring and supervision of the immunization activities.
  - Conduct post supplementary immunization activities coverage evaluation survey and implementing mop-up activities where needed.
- Improving immunization data quality
  - Review data sources for population denominators, especially for non-national populations, and use the most accurate and up-to-date figures to calculate administrative immunization coverage.
  - Conduct periodic validation of the measles vaccination coverage data using Data Quality Self assessment (DQS) every 2–3 years and coverage evaluation surveys every 5 years.
  - Improve human resource capacity for immunization data management, data analysis and interpretation and using data for action.
- Strengthening measles/rubella surveillance
  - Strengthen all aspects of measles/rubella case-based laboratory surveillance, especially the procedure for case investigation and filling in the case investigation form. Ensure availability of trained staff for this purpose.
  - Kuwait is the only country of the Region which has not reported any data to the Regional Office in 2014. Kuwait should ensure

regular reporting of measles/rubella surveillance data to the Regional Office.

Lebanon

Despite the significant reduction in measles cases in 2014 compared to 2013, Lebanon needs to exert additional efforts to control the ongoing measles outbreak and prevent occurrence of periodic outbreaks in order to achieve measles elimination.

- Improving routine vaccination coverage of MCV
  - Monitor the Penta1-MCV1 and MCV1-MCV2 dropout rate and implement appropriate measures to minimize drop out, including proper implementation of the RED approach, raising population awareness and tracing defaulters.
  - Ensure better collaboration of the private sector in providing measles vaccination as per the national schedule.
- Strengthening measles/rubella surveillance
  - Enhance involvement of the private sector in the measles/rubella surveillance system.
  - Expand zero reporting to all reporting sites.
  - Improve involvement of the school health programme in the weekly reporting system.

Libya

Despite the reported high routine vaccination coverage, Libya is repeatedly exposed to measles outbreaks. Libya should undertake more efforts in the following areas.

- Improving routine vaccination coverage of MCV: proper implementation of the RED approach, raising population awareness and tracing defaulters
- Improving immunization data quality
  - Validate the measles vaccination coverage data using data quality self assessment (DQS) and/or coverage evaluation surveys where possible.

  - Strengthen national capacity for immunization data management, data analysis and interpretation and using data for action.
- Conducting national or subnational supplementary immunization activities using MR/MMR in order to curb the current outbreak
  - Target appropriate age group(s) based on the epidemiology of measles and rubella in the country and analysis of the gaps of vaccination coverage of the past few years.
  - Ensure high quality supplementary immunization activities through proper timely planning, adequate microplanning, optimum implementation, monitoring and supervision, and ensure adequate preparation for the supplementary immunization activities using an appropriate readiness assessment dashboard throughout all phases of the preparation.
  - Conduct post supplementary immunization activities coverage evaluation survey and implement mop-up activities where needed.
- Strengthening measles/rubella surveillance
  - Strengthen all aspects of measles/rubella case-based laboratory surveillance, especially the procedure of case investigation and filling in the case investigation form and specimen collection and transfer.
- Human resource capacity-building in all areas of EPI, including measles/rubella surveillance, control and elimination.

Morocco

- Implement the second phase of the MR supplementary immunization activities as planned by Q4 2015, in order to consolidate measles/rubella elimination activities and interrupt endemic measles transmission by end 2015. Ensure high quality of the supplementary immunization activities through proper timely planning, adequate microplanning, communication and social mobilization, implementation of appropriate strategies to reach the target population and monitoring the preparation of activities using the

appropriate readiness assessment dashboard throughout all phases of the preparation.
- Establish a national expert committee to ensure high quality measles case classification.
- Establish a national measles/rubella elimination verification committee as soon as possible and begin its operation in 2015.

Oman
- In view of the measles outbreak in 2014 in a population that was missed during previous measles supplementary immunization activities, search for other population groups that could have missed vaccination and implement catch-up vaccination schedule for older age groups as necessary.
- Continue to update measles/rubella case classification in accordance with WHO framework for verifying the elimination of measles and rubella.
- Establish a National Measles/Rubella Elimination Verification Committee as soon as possible and begin its operation in 2015 to prepare the reports to the regional verification commission to verify elimination.

Pakistan
- Improve routine vaccination coverage of MCV through proper implementation of RED approach, raising population awareness and defaulter tracing. Monitor the Penta1-MCV1 and MCV1-MCV2 dropout rate and implement appropriate measures to minimize drop out, including defaulter tracing.
- Ensure proper planning and implementation of the measles supplementary immunization activities in the remaining provinces and use the appropriate readiness assessment dashboard to ensure adequate preparation.
- In view of the results of the post supplementary immunization activities coverage survey in Sindh, showing coverage less than 80%

in 17 of 18 townships/district s of Karachi, implement measles mop-up vaccination activities, with emphasis on achieving high quality, in those low performing districts/ townships. The same action should be taken for all other provinces when results of the post supplementary immunization activities coverage surveys are available.

- In view of the low measles surveillance performance indicators, strengthen measles/rubella case based laboratory surveillance through:
  - Extensive training of health workers on measles/rubella surveillance and case investigation
  - Raising awareness among all health professionals on the importance of reporting all fever/rash suspected cases with adequate investigation and collecting adequate specimens from all cases.

Palestine

- Expand the reporting sites to include the private sector.
- Improve the functionality of the measles expert committee. Consider replacing inactive members to ensure regular meetings of the expert committee.

Somalia

- Improve routine vaccination coverage of MCV through proper implementation of the RED approach with adequate implementation of a proper communication and social mobilization strategy.
- Ensure proper planning and implementation of the catch-up supplementary immunization activities planned for 2015 to ensure reaching high coverage in all accessible areas, with emphasis on the following:
  - targeting appropriate age groups based on the epidemiology of measles
  - allocating adequate time for planning, adequate microplanning and optimum implementation, monitoring and supervision, using

the appropriate readiness assessment dashboard throughout all phases of the preparation
- conducting post supplementary immunization activities coverage evaluation survey and implementing mop-up activities where needed.

- Strengthen the measles laboratory case-based surveillance system by utilizing the polio infrastructure.

Sudan

Despite the significant reduction in measles cases in 2014 compared to 2013, Sudan needs to exert additional efforts to improve population immunity.

- Strengthen routine immunization with the 2 doses of the MCV, through proper implementation of the RED approach, monitoring the Penta1-MCV1 and MCV1-MCV2 dropout rate and implementing appropriate measures to minimize the dropout rate, including raising population awareness and tracing defaulters.
- Ensure timely implementation of high quality follow-up supplementary immunization activities.
- Further strengthen measles surveillance, expand it to cover all health facilities and engage the private sector.

Syrian Arab Republic

- Intensify efforts for strengthening routine immunization and rebuilding the EPI infrastructure.
- Ensure regular availability of measles-containing vaccine and expedite registration of available WHO prequalified vaccines.
- Implement high quality follow-up measles supplementary immunization activities at short intervals to bridge the gap resulting from low routine vaccination coverage.

Tunisia

- Ensure proper case/outbreak investigation to identify any gap in population immunity to consolidate the progress towards interruption of endemic virus transmission.
- Conduct advocacy for involvement of the private sector in measles case-based surveillance.

Yemen

- Improve routine vaccination coverage of MCV through proper implementation of the RED approach, monitoring the Penta1-MCV1 and MCV1-MCV2 dropout rate and implementing appropriate measures to minimize drop out through raising population awareness and tracing defaulters.
- With implementation of MR supplementary immunization activities, introduce MR vaccine into routine immunization as soon as possible to avoid accumulation of susceptible populations and shifting of the age group.
- Implement follow-up supplementary immunization activities at the appropriate time based on through analysis of routine vaccination coverage and measles/rubella cases at governorate and district levels.
- Ensure availability of funds for regular procurement of MR vaccine.
- Conduct proper rubella case investigation and follow-up on the cases among pregnant women.
- Establish and strengthen CRS surveillance.

World Health Organization

REGIONAL OFFICE FOR Europe

Extraordinary meeting of the European Technical Advisory Group of Experts on Immunization (ETAGE)

30 January 2015

ABSTRACT

The European Technical Advisory Group of Experts on Immunization (ETAGE) met on 30 January 2015 to review and discuss measles and rubella elimination in the WHO European Region and to be briefed and provide input on the advocacy plan for the European Vaccine Action Plan (EVAP).

Representatives of the European Regional Verification Commission (RVC) participated at the meeting, to report on their November 2014 review of regional measles and rubella elimination progress as reported by Member States for 2013.

Keywords

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Introduction

The European Technical Advisory Group of Experts on Immunization (ETAGE) meets annually to review the progress of the Vaccine-preventable Diseases and Immunization Programme (VPI) towards the European Region's disease prevention goals. ETAGE usually meets on an annual basis, during the third quarter of the year. At its 14th meeting, conducted 8–9 October 2014, ETAGE supported several changes to the verification process for the elimination of measles, related to reporting at country level and the categorizing of Member States according to their elimination status. Recognizing the need for further discussion and development of indicators, ETAGE called for an extraordinary meeting: to consider more complete data on the status of regional measles and rubella elimination (based on the outcomes of the RVC meeting to be held November 2014); to develop specific recommendations for furthering the verification initiative; and to provide input related to advocacy of the European Vaccine Action Plan (EVAP). The extraordinary meeting was conducted on 30 January 2015 at the WHO Regional Office for Europe (Regional Office), Copenhagen, Denmark.

Representatives of the RVC participated in the extraordinary meeting, to report on their November 2014 review of regional measles and rubella elimination progress as reported by Member States for 2013.

Opening remarks

Mr Robb Butler, acting Programme Manager of the Vaccine-preventable Diseases and Immunization Programme (VPI), welcomed participants on behalf of the WHO Regional Director and provided an overview of the scope and purpose of the meeting. Professor Pierre Van Damme welcomed participants on behalf of ETAGE and expressed appreciation for the opportunity to bring together members of ETAGE and the European Regional Verification Commission (RVC) to review the current status of measles and rubella elimination in the Region and discuss possible changes to the verification process.

Measles and rubella elimination: regional verification status, 2013 reports, conclusions and follow-up action

Dr Susana Esposito, RVC Chair

The RVC met for the third time on 10–12 November 2014 in Copenhagen, Denmark when the 8-member panel evaluated a total of 59 country reports. These included Annual Status Updates (ASU) for 2013 and late-submitted Elimination Status Reports (ESR) for 2010–2012.

Member States are required to form a National Verification Committee (NVC) for measles and rubella elimination. To date, 50 out of 53 Member States have established an NVC, and of these, 46 submitted ASUs for 2013.

Criteria for documenting the verification of interruption of endemic measles and rubella transmission include the absence of endemic measles and rubella cases in the presence of a high-quality surveillance system, supported by genotyping data on measles and rubella virus isolates. Supporting evidence submitted by the NVC to the RVC includes the epidemiology of measles, rubella and congenital rubella syndrome (CRS), molecular epidemiology of measles and rubella

viruses, performance of measles, rubella and CRS surveillance systems and population immunity against measles and rubella, including data from vaccination coverage surveys, vaccine registries and serosurveys.

In reviewing the 2013 reports, the RVC encountered similar issues and deficiencies to those encountered with the ESR 2010-2012 submission: incomplete information, particularly regarding laboratory activities, misinterpretation of data requested and inappropriate use of denominators for the estimation of vaccination coverage. Miscalculations and the inadequate presentation of data, particularly with regard to surveillance indicators, were also common. Completeness of the ASUs was generally high, although some countries omitted important information or details. It appears that a significant minority of countries did not completely understand the requirements or lacked the resources to provide all of the requested data.

For several countries, information on the quality of surveillance indicators was either absent, incomplete or not submitted correctly. Confusion continues on the part of some Member States over the definition and method of calculation of the sensitivity of surveillance. Sensitive surveillance is defined as the detection of >2 suspected cases per 100 000 population. In the absence of confirmed cases, a sensitive surveillance system is expected to document 2 or more discarded cases per 100 000 population (the 'discard rate'). Of the 35 countries reporting a discard rate, only 11 reported a rate of >2 per 100 000 population.

Ten Member States did not have a status report reviewed by the RVC, including 7 that failed to submit any report and 3 that have been requested to revise and resubmit their reports due to missing information.

Several Member States lack the capacity to document virus transmission pathways, due to the absence of sufficient genomic sequence data and failure to effectively implement surveillance by linking clinical, epidemiological and laboratory data. As the Region moves towards the measles and rubella elimination goal it is essential that all Member States report genomic sequence data on viruses isolated or detected and that the capacity to integrate these data unequivocally to the surveillance case records is significantly strengthened.

Every Member State should establish a National Plan of Action for measles and rubella elimination and should report details of this Plan to the RVC. As of the end of 2014, 27 countries had a current Plan of Action; 3 countries had plans that were time-expired; 4 had plans in development; and 19 Member States failed to report on the status of their plans.

With regard to measles, the RVC concluded that 22 Member States had interrupted endemic transmission in 2013, 7 of which were at risk of re-establishing transmission due to suboptimal population immunity, and that 13 countries remained endemic. Measles elimination status was inconclusive for 8 countries due to insufficient evidence being provided; and the status of 10 countries was not reviewed due to lack of adequate reports. For rubella, the RVC concluded that 24 Member States had interrupted endemic transmission in 2013, 7 of which were at risk of re-establishing transmission, and that 9 countries remained endemic. Rubella elimination status was inconclusive for 10 countries, and the status of a further 10 countries was not reviewed. Overall, the status of measles and rubella elimination in the Region in 2013 was very similar to that seen in 2012.

Discussion

While the number of countries in the Region that have interrupted transmission is relatively high (22 for measles and 24 for rubella), this encompasses many of the small- to medium-sized countries. The countries with the largest populations remain endemic for either measles or rubella, or both. It would be helpful if the tables showing the grouping of countries by level of achievement could include an indication of the total population represented at each level.

WHO headquarters provides general guidance and standards for its regional offices to follow, but the individual regions are free to develop their own strategies and systems for validation of elimination. Of issue for the RVC is the apparent lack of pressure placed on Member States to comply with regional verification requirements, as witnessed by the lack of reports from several countries. It is possible that greater political commitment could be generated among Member States if WHO headquarters played a more prominent role in pushing countries towards measles and rubella elimination.

There is an increasingly urgent need for the regional programme to demonstrate that progress is being made towards measles and rubella elimination in some Member States, and also to encourage more action among those that are not showing sufficient progress towards the elimination goals.

Measles and rubella elimination: epidemiology, operationalization of modified verification process, VPI mobilization plan for 2015

Dr Abigail Shefer, WHO Regional Office for Europe

Measles and rubella epidemiology in 2014

Data for 2014 suggest that there may have been a substantial reduction in the number of measles cases in the Region compared with 2013 (provisionally 15 445 in 2014 against 32 171 in 2013). Most of the reported cases in 2014 occurred in Bosnia and Herzegovina, Georgia, Italy, Russian Federation and Ukraine. The regional total of rubella cases in 2014 also appears to be a reduction over 2013 (provisionally 6 257 in 2014 against 39 562 in 2013), with very large outbreaks, primarily in Romania and Poland through 2012 and 2013, now showing signs of dying out. As of November 2014, Poland has reported approximately 90% of all cases in the Region in 2014.

In several Member States many adults continue to be infected, with 41% of regionally reported measles cases being ≥ 20 years of age. A number of countries (Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Turkey and United Kingdom) have, or will very shortly, conduct supplementary immunization activities (SIAs) in response to outbreaks of measles. There are recognized ongoing measles outbreaks in Bosnia and Herzegovina, Kazakhstan and Kyrgyzstan.

Operationalization of modified verification process

It has been proposed that a system of grouping Member States according to level of achievement be adopted. The advantages of categorizing countries in this way include providing a mechanism for prioritizing countries according to need for support and introducing an element of competition between countries to achieve elimination status. This should make it easier to highlight those countries considered to be better performers and those considered to be at risk. It may also make it easier for RVC members to work with a group of countries that have the same status and similar circumstances.

Proposed achievement categories:

- countries with interrupted transmission ≥ 36 months (verified as having achieved elimination);
- countries with interrupted transmission < 36 months;
- countries with endemic transmission (re-established);
- countries with endemic transmission (never interrupted);
- inconclusive (e.g. due to poor quality, inconsistent or incomplete data);
- not reviewed by the RVC (due to lack of or insufficient reporting).

This categorization can be linked to a colour system, indicating which countries have moved up the scale in the past year, those that have not been reviewed in the past year and those that have moved down the scale.

The second proposed change to the verification process is to verify elimination of measles and rubella at country level, rather than only at regional level. This strategy has been adopted by the WHO Western Pacific Region and there is an opportunity to learn from experience gained there.

VPI mobilization plan for 2015

Building on the Package for Accelerated Action: 2013-2015, VPI developed a proposed measles and rubella mobilization plan encompassing measles and rubella elimination activities for 2015. The plan focuses on specific actions to build the capacities of Member States to address remaining challenges. The primary goals are:

- to improve Member States' understanding of the verification process and thereby improve the quality of reporting;
- to address country-specific challenges through country support missions; and
- to increase impact through categorization of countries and consistent messaging.

Planned activities to improve the quality of reporting by NVCs include the staging of a series of intercountry workshops planned for March to May 2015 to include all Member States in the Region. The first workshop is intended for Member States of the European Union and European Economic Area (EU/EEA) (24–25 March), the second for selected newly independent states (NIS), and the third for non-NIS, non-EU/EAA countries. NVC chairpersons together with national surveillance technical experts will be invited to these meetings and the focus will be on the challenges encountered in surveillance and data management. The meetings will include practical sessions on the updated reporting forms and technical support will be provided in understanding and completing the forms. Depending on needs and capacities, VPI will consider country missions as an alternative for some Member States.

VPI also proposed that a pre-review process be introduced for all country annual reports prior to the formal RVC review. The pre-review would be conducted by members of the RVC and WHO Secretariat to identify reports that require clarification, additional information or correction before they are formally submitted for RVC analysis. This will require submission of annual update reports early enough in the year to allow for this extra step.

To address country-specific challenges through country support missions, Member States have been classified according to priority for support. Eleven countries have been classified as being of high priority for support missions, and these will be visited or will have a visit date scheduled during the first quarter of 2015. Fifteen countries are considered to be of medium priority and

plans are being developed to visit these by the end of the second quarter of 2015. It is expected that a further 11 countries, considered to be of lower priority, will be visited before the end of 2015. The goal of country support missions is to address political, technical or high-level advocacy needs and the mission team composition will reflect the type of support required. There are currently 10 missions planned for the first quarter of 2015, 5 planned for the second quarter, 5 for the third quarter and 6 for the fourth quarter of 2015. In addition to these missions, high-level advocacy missions are planned for Austria, France, Italy, Poland, Romania and Ukraine.

Population immunity profiles

Dr Sebastian Funk, London School of Hygiene and Tropical Medicine

A project conducted by the London School of Hygiene and Tropical Medicine in coordination with the Regional Office is attempting to determine if the annual data reported to WHO through the WHO/UNICEF Joint Reporting Form (JRF) and other data sources can be used to estimate immunity gaps at population level. The number of people in a population that are susceptible to a disease depends primarily on the number of people that have already contracted the disease and the number that have been vaccinated. This information has been reported at country level, and collected at international level, since 1980, potentially allowing estimates of population immunity in any given age cohort for each country reporting data.

Plotting reported vaccination coverage against age cohort does permit detection of potential immunity gaps in a number of countries, however, the data sets are not complete for all countries for all years, and methods used for estimating vaccination coverage are not the same in all countries. To estimate population immunity the history of disease incidence also needs to be considered and this data has also been reported through the JRF. Review of available data, however, suggests that historically there has been considerable underreporting of disease. In addition, the age distribution of cases is not reported through the JRF, and in order to make use of the data, estimated age distributions were used based on known patterns of age distributions of cases.

Using available data on vaccination coverage (from routine as well as supplementary immunization activities) and disease incidence, national susceptibility profiles can be developed, and, if the data are reliable, these demonstrate which countries have significant susceptible populations and which age cohorts represent the greatest risk. Predicted immunity gaps can potentially be validated by assessing which age groups are infected during an outbreak. However, it appears that for a variety of reasons the number of individuals infected in the youngest or oldest age cohorts may generally be underestimated. Another method for validating predicted immunity gaps is to make a comparison with available serological surveillance data, although the utility of this approach may be questionable given the difficulties of using historical data to determine the fraction of individuals in previous cohorts who were infected.

Another source of data to consider is the European Sero-Epidemiology Network (ESEN2), which was established in 2001 with the aim of standardizing the serological surveillance of 8 vaccine-preventable diseases in 22 European countries. Serological data generated through ESEN2 for the years 2002 and 2003 were compared with the predicted immunity profiles generated from the JRF data, and used to estimate the extent of disease underreporting. Using this method it appears that underreporting was minimal in several countries, but that many countries failed to report a

significant proportion of cases ranging from less than 10 to several hundreds of cases for every reported case.

In comparison with the immunity gaps identified through the RVC review process, this analysis found an additional 8 countries with potential gaps in immunity (i.e. with the RVC conclusion of interrupted transmission but not at risk). The limitations in interpreting these analyses remain significant due to missing and poor-quality data, particularly for adult populations.

Discussion

Improving the quality of reporting has been a goal for several years now, and a significant level of activity has taken place to attain this goal. However, even if can be attained high quality current reporting, it is still could not possible to demonstrate how many susceptibles there are in a country, and to which age groups they belong, as the historical case data are usually subject to significant and unknown levels of underreporting. While it is clearly essential to improve the quality, there were significant questions regarding what evidence, in addition to vaccination coverage and surveillance data, could be collected in order to accurately assess the status of a country's elimination status. While country support missions are clearly necessary, it is possible that, due to lack of good-quality data, the real problems faced by a country are not being exposed and cannot, therefore, be addressed. ETAGE was concerned that some level of re-thinking of the process for acquiring accurate and relevant information on the status of measles and rubella elimination in countries is required.

The importance and relevance of serological assessments in determining susceptibility to measles was discussed at length. While vaccine coverage estimates provide a measure of the level of susceptibility of vaccine-receiving younger age cohorts, they provide no information on susceptibility of older age cohorts, including adults, who did not receive vaccines through routine immunization. The only way to demonstrate susceptibility gaps in these age groups is to conduct appropriate serosurveys. Although serosurveillance data are relatively easy to obtain and interpret in some countries, there remain considerable difficulties in both obtaining and interpreting serological data in many countries, including some of those considered to be of highest priority. Regional guidance on serosurveys was published last year and new global guidelines on conducting serosurveys and use of serosurveillance data are being prepared by WHO. A draft will be available for comments very soon. Assessment of available serosurveillance data should be included in the country review process and used to support countries in strengthening their immunization programmes. ETAGE proposed that standardized serosurveys should be established across Europe, following in from the ESEN2 Project, to identify measles and rubella susceptibility pockets.

It was generally accepted that there has been lack of progress in the Region toward achieving its 2015 measles and rubella elimination goal, and questions were raised over the reasons for this. One contributing factor to the lack of progress in some countries may be the lack of a clear understanding of the respective roles of WHO and the Member States in setting and achieving the goal. The 2015 elimination goal was set by the Member States, and commitment for achieving the goal must come from them. The role of WHO is to support Member States in realizing the goal, by providing technical support and high-level advocacy. Use of experts from successful countries to share experiences with less successful countries may provide encouragement for improved commitment and performance.

Measles and rubella elimination goal, 2015: communications, advocacy and reputational risk management issues

Mr Robb Butler, WHO Regional Office for Europe

The 2010 regional goal for measles and rubella elimination passed without attracting a great deal of attention. It is now generally considered that the 2015 regional elimination goal will also not be met, but there is a determination within WHO that failure to meet the 2015 goal will not be allowed to pass without a significant effort to strengthen programme performance and make elimination a realistic short-term goal. The communications activity around the 2010 goal was probably insufficient to raise the necessary prioritization of measles and rubella in Member States, and to establish the ownership required to achieve the goal. Since then communications and advocacy activities have progressively been strengthened. A new package of accelerated action prompts have been provided since 2012, including ongoing development of resource mobilization guidelines and advocacy tools, region-wide European Immunization Week activities, risk and crisis communications support and capacity building, a scale-up of the social media platform, a number of country-level immunization communications reviews and the development of guidelines for these.

The goal of communications and advocacy now is to maintain and accelerate commitment and action for elimination from Member States through 2015 and beyond. To achieve this will require a change in the emphasis of communications activities, towards more effective highlighting of the requirements and expectations placed on Member States. New strategies and guidance on communications and advocacy are being developed that are evidence based and reflect experience gained over the past few years. New partners in measles and rubella elimination have been engaged, and the verification process has been developed and strengthened, providing new platforms from which communications can be launched.

With respect to the measles and rubella mobilization plan goal of increasing impact through effective and consistent messaging, emphasis will be placed on the progress that has been made and how close the Region now is to achieving elimination. Countries will be encouraged to maintain or improve their verification status by grouping them according to progress, publicizing their status and applauding countries that have successfully interrupted transmission of either or both diseases. A European parliamentarian roundtable event, planned for 22 April 2015 during European Immunization Week, will advocate for greater attention and commitment by decision-makers in high- and medium-priority countries.

WHO continues to introduce advocacy tools and provide training on immunization resource mobilization, advice on ring-fencing immunization budgets and advocacy for additional funding. The Regional Office also continues to offer technical assistance on communications, advocacy and capacity building and will coordinate measles and rubella messaging through European Immunization Week 2015.

The 2015 elimination goal remains achievable, but it is probably not realistic to assume it will be met. Confirmation of success or failure will not be available until the RVC has reviewed available evidence in November 2016, and the Regional Committee will not formally review the RVC decision until September 2017. This extended timeframe makes communications and advocacy requirements difficult and complex, and requires careful and thorough planning and preparation. This will require a more detailed understanding of the target audience for

communications and advocacy and greater emphasis on targeting communications to high-level decision-makers in Member States.

Discussion

The need to target specific audiences was discussed as an essential component of communications policy. The need to avoid a repeat of the experience of 2010 in allowing the missed elimination goal to pass without significant comment or action was emphasized and supported.

EVAP Advocacy Plan: channels, messaging and audiences

Katrine Habersaat, WHO Regional Office for Europe

The European Vaccine Action Plan (EVAC) plots a course towards a Region free of vaccine-preventable diseases and as such, it is essential that the Plan is both known about and understood by Member States and all who champion and promote it, and that stakeholders feel commitment and ownership to the goals set. Much of the work that needs to be done to implement the EVAP is conducted by the immunization programmes and managers, but they cannot function without a range of political decision-makers, national immunization partners and regulatory bodies, international (professional) organizations and international and regional advisory bodies and working groups, including ETAGE and the RVC. In addition to a vision, EVAP defines specific goals and objectives including disease elimination, disease control, strengthening immunization programmes and improving equitable access to vaccines. To achieve these goals and objectives it is important to promote more specific messages on the actions required or changes necessary to realize the EVAP vision.

It has been proposed that the key action points for EVAP implementation at present include the following.

- Improving data information systems. Strong and reliable monitoring and surveillance through improved quality of valid and accurate data and the use of new information technologies for collection, transmission and analysis of immunization data.
- Developing tailored and innovative strategies. Research methods and improved immunization data to monitor perceptions, knowledge and attitudes towards immunization in all population groups and, based on that, tailored and innovative strategies ensuring equitable extension of services, demand in all population groups and impactful plans for vaccine safety-related events and introduction of new vaccines.
- Establishing and strengthening independent national advisory bodies. Establishing evidence-based decision-making on immunization and providing justification for greater investment, including on new vaccines, through independent National Advisory Bodies (NITAGs).
- Increased political commitment and domestic funding. Advocacy and resource mobilization activities ensuring that national decision-makers are aware that by adopting the EVAP in 2014, Member States made an unprecedented commitment to immunization as a priority, pledging to ensure political commitment and sustainable and predictable investment in immunization.
- Strengthening regulation and procurement mechanisms. A fully functional NRA as a strong regulatory mechanism to ensure access to and use of quality-assured vaccines at

affordable prices – and an efficient procurement system with predictable, transparent pricing and innovative procurement mechanisms to alleviate funding pressure.
- Improving monitoring and surveillance systems. Case-based surveillance and Adverse Events following Immunization (AEFI) surveillance systems, a strong expert review committee assessing causality for AEFIs and sustained access to WHO-accredited polio and measles-rubella laboratories.

Five platforms for advocacy have been identified: WHO activities, i.e. provision of knowledge and technical support to Member States in implementing the Plan; national EPI programmes and managers who advocate on behalf of immunization at national level; WHO communication channels, including websites and social media; external communication channels, including peer-reviewed publications, partner publications and other health or immunization-related publications; and partners, including international organizations and international and regional advisory bodies and working groups. ETAGE members in particular are seen as a potentially very valuable group of advocates.

ETAGE members can potentially advocate for EVAP by integrating the Plan into their work, presentations, teaching and workshops; developing professional relationships with national stakeholders; providing technical support documents; demonstrating good practice; engaging in social media activities; and using every opportunity to promote and advocate on behalf of the EVAP. ETAGE members were asked to discuss how VPI could best support them in promoting and advocating for EVAP, e.g. by providing standard and up to date presentation materials; and providing technical documents with messages, guidance and appropriate infographics.

Discussion

ETAGE noted and approved of more recent Regional Office undertakings to actively engage its members over the past few years and encouraged the Secretariat to consider increased involvement of ETAGE in support of Member States. Provision of updated presentation materials has been very useful at national and professional level, particularly for meetings with NITAGs, in promoting and advocating for EVAP, and the Secretariat was encouraged to continue to provide and update these materials. There is a professional interest within the Region in receiving current information on the vaccine-preventable diseases programme, and ETAGE can play a role in providing this information through scientific meetings and seminars. ETAGE members can also play an important role in advocating for immunization during missions to countries, not only with the technical authorities and bodies but also with high-level political decision-makers.

The WHO Regional Office and its programmes tend to have low visibility for journalists and the general media. Greater efforts should be made to describe and promote the activities conducted and achievements made within the Region. ETAGE members are often highly visible within their own countries, and generate interviews and talks describing their own work. With little additional effort these opportunities could include some elements of advocacy for EVAP and promotion of regional plans and achievements. More effective use could also be made of existing infographics by putting together a package of materials for journalists to explain and promote EVAP.

Further discussions are required on the nature and format of materials required for more effective promotion of WHO and regional programme activities. Other WHO regions, PAHO for example, have been addressing this issue for some time and may be able to offer advice based on their

experiences. It may be possible to include this topic on the agenda of the next post-SAGE meeting for TAG members.

Closing discussions

ETAGE has greatly appreciated the opportunity to hold the extraordinary meeting, permitting consideration of aspects of the measles and rubella elimination programme in greater detail than is usually possible in the annual ETAGE meetings. ETAGE also appreciates VPI's efforts to generate a better overview of immunity gaps in the Region, particularly the development of diseases-susceptible adult cohorts as immunization has been introduced over the years. This information is highly valuable for Member States to identify at risk populations.

This has been a very good opportunity for ETAGE to meet with members of the RVC and to gain a better understanding of the role played by the RVC. Further efforts are clearly necessary to improve the quality of data being submitted to the RVC. ETAGE supports proposals to develop further tools and strategies to encourage provision of accurate and reliable information on the status of measles and rubella elimination. ETAGE strongly recommends the use of additional information, such as the results from serosurveys, to support vaccine coverage and disease surveillance data in establishing the risk of outbreaks occurring in a particular country. The added value of categorizing countries into groups dependent on the level of achievement has been discussed at an earlier meeting and the proposal has now been further developed. Further development should take into account assessment of additional information provided by countries, including seroepidemiological data if this is available.

The relative roles and responsibilities of the WHO Regional Office and WHO headquarters, with regard to establishing plans and developing strategies, are not clearly understood by ETAGE and further explanation would be helpful. What was clear to ETAGE is that the elimination goal supported by WHO is a goal of the Member States, not a goal of WHO. Member States should be made more aware of their roles and responsibilities in achieving the goals they have agreed to and that the role of WHO is to support Member States in achieving their goals.

ETAGE noted and approves of the markedly increased activity in advocacy and communications activities and tools developed by the Regional Office in the past 5 years. The entire communications landscape has changed dramatically over the past 5 to 10 years and WHO has invested heavily in the development of new tools of communication and developing new partnerships in communications and advocacy. Communications on maintaining the 2015 deadline for regional measles and rubella elimination presents a complex and difficult challenge that will need to be addressed to take advantage of all of the gains made by the end of 2015 if elimination is not achieved. ETAGE has an important role to play in advocacy and communications and ETAGE members can play a more active part in promoting the programme.

Draft conclusions and recommendations

ETAGE greatly appreciated the opportunity to hold the extraordinary meeting and the opportunity to become better acquainted with the objectives, activities and members of the RVC. It also appreciated the opportunity to gain a better understanding of the importance of determining measles and rubella susceptibility profiles in populations with established immunization programmes, particularly on the generation of disease-susceptible age cohorts.

ETAGE fully supports VPI's mobilization plan for 2015 and agrees with the proposed activities and timeline for implementation. Further efforts are clearly necessary to improve the quality of data being submitted to the RVC, and ETAGE supports proposals to develop further tools and strategies to encourage provision of accurate and reliable country information.

ETAGE suggests that consideration be given to implementation of a standardized serosurvey process in the Region, such as ESEN3. Further discussion is recommended to weigh the benefits and resources needed to implement such an initiative.

ETAGE supports increasing advocacy activities to ensure that national decision-makers are fully aware that by adopting the measles and rubella elimination goal Member States made a commitment to ensure political commitment and investment to achieve the goal.

ETAGE noted and approves of the markedly increased activity in advocacy and communications activities and tools developed by the Regional Office in the past 5 years. As the communications landscape has changed over the past 5 to 10 years WHO has invested heavily in the development of new tools of communication and new partnerships in communications and advocacy.

Recommendations

- Member States should be reminded that the regional measles and rubella elimination goal belongs to the Member States, not to WHO. All Member States should ensure they have the political commitment required to prioritize measles and rubella elimination and achieve the goal.
- Use should be made of additional country information, such as the results from serosurveys, to support vaccine coverage and disease surveillance data in establishing the risk of outbreaks in a particular country due to immunity gaps. Recognizing that due to poor historical data on cases the only effective way to do this is to implement a standardized process for conducting serosurveys across the Region (e.g., ESEN3).
- As also noted in the 2014 meeting report, ETAGE agrees with and recognizes the added value of categorizing countries into groups dependent on the level of achievement towards elimination status and verifying elimination at the country level.
- Further refinement and development of this approach should take into account the assessment of additional information provided by countries, including seroepidemiological data if this is available.
- Recognizing the important role ETAGE can play in advocacy and communications and in promoting programme goals, further detailed discussion is required on the potential roles and inputs of ETAGE, beyond the technical inputs to programme development.

Annex 1. List of participants

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Summary of the December 2014 Gavi Alliance Board Meeting

In December 2015, the GAVI Alliance Board made a number of decisions and recommendations summarised below:

Ebola - the Gavi Board endorsed a commitment of up to US$300M for procurement of Ebola vaccines pending WHO recommendations. In addition up to US$90M to support countries introduce the new vaccines and rebuild the health system. The release of funds will be done under the oversight of the Executive Committee (EC) following the WHO recommendations. The Board noted that to meet the funding requirements of the Ebola Envelope, Gavi could use a combination of existing and new sources of funds and join forces with initiatives which have already pledged funding to address the Ebola crisis.

In light of the rapidly evolving nature of Ebola vaccine development, the Board resolved that there be a special convening of the EC by teleconference in January 2015 and February 2015 and an update to
the Board at their retreat in March 2015. The Board could then review the status and progress, especially any new data regarding clinical trials, efficacy, and other strategic issues, and discuss any needed adjustments or decisions regarding the way forward .

The Board also noted its support for funding a potential stockpile for second generation Ebola vaccines, designed according to WHO-convened guidance, and related maintenance and operational costs, and requested the Secretariat to explore the associated financial implications.

Replenishment - a number of donors confirmed their commitments to Gavi in advance of the Berlin conference amounting to about 55% of the total ask of US$7.5 bn. There seems to be a lot of optimism in mobilizing resources close to the target. Major commitments for 2016-2020 to date include EUR 500 M from Germany, CAD 500M of Canada, US1Bn form the UK and the IFFim bond which raised US$500M. A number of new donors have indicated commitments to pledge in Berlin including Saudi Arabia, Qatar and UAE. The dialogue with China continues, on engaging more Chinese vaccine manufacturers as well as Gavi's potential influence over China's domestic EPI policy. Additional and separate announcements are expected on Ebola including from the ADB.

Governance - the Board confirmed the nomination of Dr Flavia Bustreo, WHO's Assistant Director General for Family, Women's and Children's Health as Vice Chair of the Board, Chair of the Governance Committee and Vice Chair for the Executive committee for the term of 1 January 2015 to 31 December 2016.

Risk Management - a new policy for risk management was endorsed strengthening request by donors for Gavi to differentiate fiduciary risk from programmatic risk.

Business Plan 2015 - the Gavi Board approved US$250M for supporting the Secretariat and implementing partners to the Gavi business plan. Furthermore, discussions were initiated for changing the current operating model to support the implementation of the 2016-2020 approved strategy to one that is more country focused.

Finally to note the Board discussed the GVAP progress report with interest in re engaging in a joint dialogue on the lagging goals and with the most critical countries and key immunization partners.

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Global Advisory Committee on Vaccine Safety, 3–4 December 2014

The Global Advisory Committee on Vaccine Safety (GACVS), an international expert clinical and scientific advisory body, was established by WHO to provide independent, scientifically rigorous advice on vaccine safety issues of potential global importance.[1] GACVS held its 31st meeting in Geneva, Switzerland, on 3–4 December 2014.[2] The Committee reviewed issues concerning monitoring of the safety of novel vaccines against dengue, malaria and Ebola virus. It also reviewed methodological issues related to the performance of vaccine safety surveillance systems, the assessment of website content for inclusion in the Vaccine Safety Net, and enhancing the standardization of vaccine safety surveillance for vaccines used during pregnancy.

Preparing for dengue vaccine introduction

Large scale phase 3 clinical evaluation of a tetravalent live recombinant dengue vaccine (CYD-TDV, Sanofi-Pasteur) in >30 000 individuals from Asian and Latin American countries confirm its protective efficacy.[3, 4] Safety data from the clinical studies indicate that local and systemic adverse reactions are comparable to those recorded for other available live attenuated

[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 Children's Hospital, Basel, Switzerland; Wellcome Trust and London School of Hygiene and Tropical Medicine, London, United Kingdom; University of Colorado, Aurora CO, USA; University of Maryland School of Medicine, Baltimore MA, USA; Centers for Disease Control and Prevention, Atlanta GA, USA; PATH, Washington DC, USA; GSK Biologicals, Wavre, Belgium; NewLink Genetics, Ames IA, USA.

[3] Capeding et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. Lancet 2014; 384:1358-65.

[4] Villar et al. Efficacy of a tetravalent dengue vaccine in children in Latin America. NEJM e-pub 3 November 2014.

Comité consultatif mondial de la sécurité vaccinale, 3-4 décembre 2014

Le Comité consultatif mondial de la sécurité vaccinale (GACVS), organisme international composé d'experts cliniques et scientifiques, a été créé par l'OMS pour la conseiller, en toute indépendance et avec la rigueur scientifique voulue, sur les problèmes de sécurité vaccinale pouvant avoir une importance mondiale.[1] Le GACVS a tenu sa trente et unième réunion à Genève (Suisse), les 3 et 4 décembre 2014.[2] Le Comité a examiné les questions portant sur le suivi de l'innocuité des nouveaux vaccins contre la dengue, le paludisme et le virus Ebola. Il a également passé en revue les problèmes méthodologiques liés à la performance des systèmes de surveillance de la sécurité vaccinale, à l'évaluation du contenu des sites en ligne à inclure dans le Réseau pour la sécurité des vaccins, ainsi qu'au renforcement de la standardisation de la surveillance de l'innocuité des vaccins utilisés pendant la grossesse.

Préparation à l'introduction du vaccin contre la dengue

La phase 3 de l'évaluation clinique de grande ampleur d'un vaccin vivant recombinant tétravalent contre la dengue (CYD-TDV, Sanofi-Pasteur) chez >30 000 personnes dans des pays d'Asie et d'Amérique latine confirme son efficacité protectrice.[3, 4] Les données sur l'innocuité provenant des études cliniques indiquent des réactions indésirables locales et générales comparables à celles enregistrées pour d'autres

[1] Voir N° 41, 1999, pp. 337-338.

[2] Le GACVS a invité d'autres experts pour présenter et discuter les données relatives à des sujets particuliers, notamment des personnes affiliées aux organismes suivants: Hôpital universitaire pour enfants Bâle, (Suisse): Wellcome Trust et la London School of Hygiene and Tropical Medicine, Londres (Royaume-Uni): Université du Colorado, Aurora CO (États-Unis): Faculté de Médecine de l'Université du Maryland, Baltimore MA, (États-Unis): *Centers for Disease Control and Prevention*, Atlanta GA (États-Unis d'Amérique): PATH, Washington DC (États-Unis): GSK Biologicals, Wavre (Belgique): NewLink Genetics, Ames IA (États-Unis).

[3] Capeding et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. Lancet 2014; 384:1358-13565.

[4] Villar et al. Efficacy of a tetravalent dengue vaccine in children in Latin America. NEJM e-pub 3 novembre 2014.

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vaccines. No safety concerns have been identified. The safety profile of CYD-TDV reported from the 2 phase 3 studies is consistent with the phase 2b data previously published and reviewed by GACVS.[5]

Preparing for the launch of this vaccine, guidance on safety monitoring will be required. In a preliminary review of risks that should be considered the Committee noted at least 4 groups of issues: (i) the theoretical possibility of more severe dengue cases over time post-immunization due to prior stimulation of the immune system; (ii) events related to the vaccine component, in particular the genetically modified yellow fever vaccine virus; (iii) risks in populations with specific conditions (immune deficient persons, pregnant or lactating women, patients with chronic diseases); and (iv) risks related to co-administration with other vaccines as part of a national immunization programme.

Monitoring these risks will require a well-defined strategy. GACVS confirmed the broad approaches proposed earlier that include dengue fever surveillance, vaccine introduction designs that would allow for hypothesis testing, and active surveillance for selected adverse events following vaccination that could be rare but potentially severe. The Committee concluded that advice on risk management should be developed, in parallel with that of the manufacturer, in order to assist early introducing countries to assess the safety of this important new public health tool. This would include long-term collection of population based data, particularly to assess immune enhanced dengue-related events resulting from vaccination or natural infection. After introduction of CYD-TDV, the safety of the vaccine will need to be monitored closely together with its effectiveness. Due to the need to monitor possibly rare events with reliable diagnosis, it would be desirable to conduct multicentre studies.

Preparing for malaria vaccine introduction

This session continued the June 2014 discussion on preparedness for malaria vaccine introduction.[6] The safety and efficacy data from the phase 3 multicentre trial of the RTS,S/A01 vaccine (GSK Biologicals) in 11 centres in Africa were reviewed. A total of 8922 children aged 5–17 months and 6537 infants aged 6–12 weeks were randomised 1-1-1 to receive 3 doses of RTS,S/AS01 (at 0, 1, 2 months) and a booster (at 20 months), or 3 doses of RTS,S/AS01 and a non-malaria comparator vaccine, or 4 doses of comparator vaccines (rabies or meningococcus C). The children have been followed up to a median of 48 months post dose 1 for the 5–17 month-old group and a median of 38 months for the 6–12 week-old group for safety monitoring. Two safety signals were noted that had already been published in interim analyses following the primary course at 0, 1, 2 months. The first was an increased risk of febrile convulsions within 7 days of vaccination and the second was a signal of a possible increased risk of meningitis (with no clear evidence of temporal clustering after vaccina-

vaccins vivants atténués disponibles. Aucun problème d'innocuité n'a été repéré. Le profil d'innocuité du CYD-TDV ressortant des 2 études en phase 3 concorde avec les données de la phase 2b déjà publiées et examinées par le GACVS.[5]

En préparation du lancement de ce vaccin, des orientations pour le suivi de son innocuité seront nécessaires. Lors d'un examen préliminaire des risques devant être envisagés, le Comité a relevé au moins 4 groupes de problèmes: i) la possibilité théorique d'observer des cas de dengue plus sévères après la vaccination en raison de la stimulation préalable du système immunitaire; ii) des événements liés à un élément du vaccin, en particulier le virus vaccinal de la fièvre jaune génétiquement modifié; iii) des risques dans des populations présentant certains états spécifiques (sujets immunodéficients, femmes enceintes ou qui allaitent, patients atteints de maladies chroniques); et iv) les risques relatifs à l'administration concomitante avec d'autres vaccins dans le cadre d'un programme national de vaccination.

Le suivi de ces risques nécessitera une stratégie bien définie. Le GACVS a confirmé les larges approches proposées antérieurement et incluant la surveillance de la dengue, des modèles d'introduction du vaccin permettant de tester des hypothèses et la surveillance active de certaines manifestations post-vaccinales indésirables susceptibles d'être rares mais potentiellement sévères. Le Comité a conclu qu'il fallait élaborer un avis sur la gestion du risque, en parallèle avec celui du fabricant, afin d'aider les premiers pays introduisant le vaccin à évaluer l'innocuité de ce nouvel outil important pour la santé publique. Cela comportera la collecte sur le long terme des données en population, en particulier pour évaluer des événements liés au renforcement de la dengue lié à l'immunité résultant de la vaccination ou de l'infection naturelle. Après l'introduction du CYD-TDV, il faudra surveiller attentivement son innocuité de même que son efficacité. À cause de la nécessité de surveiller des événements rares possibles en s'appuyant sur des diagnostics fiables, il sera souhaitable de mener des études multicentriques.

Préparation à l'introduction du vaccin antipaludique

Cette session a fait suite à la discussion en juin 2014 sur la préparation à l'introduction du vaccin antipaludique.[6] Les données sur l'innocuité et l'efficacité provenant de l'essai multicentrique en phase 3 du vaccin RTS,S/A01 (GSK Biologicals) dans 11 centres en Afrique ont été examinées. Au total, 8922 enfants âgés de 5 à 17 mois et 6537 nourrissons âgés de 6 à 12 semaines ont été répartis aléatoirement en 3 groupes égaux recevant 3 doses de RTS,S/AS01 (à 0, 1, 2 mois) et un rappel (à 20 mois), ou 3 doses de RTS,S/AS01 et un vaccin de comparaison autre que celui antipaludique, ou 4 doses d'un vaccin de comparaison (rage ou méningocoque C). Les enfants ont été suivis sur une durée médiane de 48 mois après la dose 1 pour la tranche d'âge des 5 à 17 mois et 38 mois pour la tranche d'âge des 6 à 12 semaines pour la surveillance de l'innocuité. Deux signaux, déjà publiés dans les analyses intermédiaires suivant la première série à 0, 1 et 2 mois, ont été observés. Le premier était une augmentation du risque de convulsions fébriles dans les 7 jours suivant la vaccination et le second une possible augmentation du risque de méningite (sans que ne se dégage clairement un regroupement temporel après la vaccina-

[5] See No. 6, 2013, pp. 68–69.

[6] See No. 29, 2014, pp. 331–332.

[5] Voir N° 6, 2013, pp. 68-69.

[6] Voir N° 29, 2014, pp. 331-332.

tion). The company also presented a risk management plan and a post-approval monitoring plan. For the latter, it is planned to establish cohort event monitoring at a number of sites in Africa. This method would be used to collect background rates for adverse events of particular interest and malaria incidence data from a cohort of about 40 000 children in advance of vaccine introduction. Subsequently, event monitoring would continue following the introduction of the vaccine. In addition, during the study period, hospital-based surveillance would be used to identify severe adverse events of interest after vaccination . As well as for febrile convulsions and meningitis, the study would monitor for potential immune mediated diseases (PIMD). GACVS noted that while the planned post-licensure studies would enable further characterization of the febrile convulsion risk, and compare meningitis rates before and after vaccine introduction (although this may be affected by meningitis epidemics), these studies would be unlikely to identify potential risks associated with very rare diseases such as certain PIMDs unless those risks were large.

Following the company's presentation, GACVS considered progress on the development of guidance by WHO on post-licensure safety surveillance for the RTS,S/AS01 malaria vaccine in special studies. The proposed approach is to study the signals identified during clinical trials and lists the events of interest for post-licensure surveillance. It also summarizes possible designs and settings for special studies of those outcomes of interest. GACVS discussed the potential difficulties in accurately identifying rates of febrile seizures without active follow-up as they are transient and may not always present to health-care facilities. As the febrile seizure risk has already been identified and quantified in pre-licensure clinical trials (and is statistically significant in self-controlled case series secondary analysis), prioritization of limited post-licensure study resources towards more severe outcomes may be appropriate. For certain outcomes, efficiency might be garnered by planned meta-analysis of pre- and post-licensure data collected using similar protocols.

Guidance on monitoring adverse events of special interest should be tailored to take into account the resources and infrastructure expected to be available in early introducer countries, maximizing synergies when possible. For example, in the case of meningitis, there is a well-established surveillance network in the meningitis belt countries that could provide reliable case validation, if RTS,S vaccination status could also be ascertained. To facilitate application of the guidance, protocols for each condition of interest should be developed jointly with clinicians and epidemiologists active in the countries under consideration. For PIMDs in particular, GACVS is concerned that many countries which will introduce malaria vaccine have insufficient capacity for identifying the majority of those events. It is recommended that a consultation be organized with experts from implementing countries

tion). La société a également présenté un plan de gestion du risque et un plan de suivi post-homologation. Pour ce dernier, il est prévu d'instaurer une surveillance des événements dans des cohortes sur un certain nombre de sites en Afrique. Cette méthode sera utilisée pour obtenir les fréquences spontanées des événements indésirables ayant un intérêt particulier et les données sur l'incidence du paludisme dans une cohorte d'environ 40 000 enfants préalablement à l'introduction du vaccin. Par la suite, le suivi des événements se poursuivra après l'introduction du vaccin. De plus, au cours de la période de l'étude, la surveillance dans les hôpitaux sera utilisée pour repérer les événements indésirables graves après la vaccination présentant un intérêt. En plus des convulsions fébriles et de la méningite, l'étude surveillera des maladies potentielles à médiation immunitaire. Le GACVS a relevé que, si les études post-homologation prévues allaient permettre de caractériser davantage le risque de convulsions fébriles et de comparer les taux de méningite avant et après l'introduction du vaccin (bien qu'ils puissent être affectés par les épidémies de méningite), il était peu probable qu'elles identifient les risques potentiels liés à de très rares affections, comme certaines maladies potentielles à médiation immunitaire, sauf si ces risques sont importants.

Après l'exposé de la société, le GACVS s'est penché sur les progrès accomplis dans l'élaboration par l'OMS d'orientations sur la surveillance de l'innocuité après l'homologation du vaccin antipaludique RTS,S/AS01 au moyen d'études spéciales. L'approche proposée consiste à étudier les signaux repérés lors des essais cliniques et à dresser la liste des événements présentant un intérêt pour la surveillance post homologation. Elle récapitule aussi les modèles et conditions possibles pour des études spéciales de ces effets présentant un intérêt. Le GACVS a discuté des difficultés potentielles pour établir précisément les taux des convulsions fébriles en l'absence d'un suivi actif, du fait qu'elles sont passagères et peuvent survenir en dehors des établissements de santé. Comme ce risque a déjà été repéré et quantifié au cours des essais cliniques avant l'homologation (et comme il est statistiquement significatif dans les analyses secondaires des séries de cas autocontrôlées), il pourrait être judicieux d'orienter en priorité les ressources limitées pour les études post-homologation sur les effets les plus graves. Pour certains résultats, l'efficience pourrait être obtenue en planifiant des méta-analyses des données avant et après homologation collectées au moyen de protocoles similaires.

Les orientations sur la surveillance des événements indésirables d'intérêt particulier doivent être adaptées pour prendre en compte les ressources et les infrastructures que l'on peut s'attendre à trouver dans les premiers pays introduisant le vaccin, en optimisant les synergies là où c'est possible. Par exemple, dans le cas de la méningite, il existe un réseau de surveillance bien établi dans les pays de la ceinture de la méningite, susceptible de fournir des validations fiables des cas, si le statut de la vaccination par le RTS,S peut également être vérifié. Afin de faciliter l'application des orientations, des protocoles pour chacune des affections présentant un intérêt devraient être élaborés conjointement avec des cliniciens et des épidémiologistes travaillant dans les pays à l'étude. Concernant les maladies potentielles à médiation immunitaire en particulier, le GACVS s'inquiète du fait que de nombreux pays qui introduiront le vaccin antipaludique manquent de moyens pour repérer la majorité de ces évènements. Il est recommandé d'organiser

to further consider what could (and could not) be identified and properly studied.

GACVS also highlighted that, as with the introduction of other vaccines, it is essential to allow for spontaneous reporting of any safety concern associated with the vaccine. This will mean reviewing existing vaccine safety monitoring systems and planning developments in order to improve upon available tools and ensure awareness of those involved with malaria vaccination. It also implies that those countries should have sufficient capacity in place to investigate cases of serious adverse events and have access to independent experts in order to assess the causal relationship between those events and administration of the vaccine.

Safety of Ebola virus vaccines

WHO actively supports and plays a key role in the coordination of vaccine development. Two Ebola virus vaccines are currently undergoing phase 1 clinical trials: ChAd3-EBO-Z (GSK Biologicals/NIAID) and rVSV-ZEBOV (NewLink/Merck). Timelines for the availability of phase 1 data and key milestones for the phase 2/3 testing were presented. Phase 3 trials for Ebola vaccines could start in early 2015 with initial safety data possibly available by June 2015. Despite the need for an accelerated vaccine development programme, the essential steps to ensure vaccine safety and quality are being followed. Vaccine quality is being overseen by good manufacturing practices committees. Ethics committees, data safety monitoring boards and other scientific boards are overseeing all trials and focusing particularly on the need for high quality of the data.

(1) The ChAd3-EBO-Z vaccine consists of a recombinant replication-defective Chimpanzee adenovirus type 3 (ChAd3) derived vector encoding the Ebola virus Zaire (EBOV-Z) glycoprotein. Preclinical data showed acute immunity against EBOV-Z with a single dose and durable immunity with a prime-boost regimen. Results were presented for the phase 1 trial VRC 207 (site: USA; product: bivalent $2x10^{10}$ and $2x10^{11}$ particle units; phase 1; n=20; start date: 2 September 2014).[7] Safety and reactogenicity data in the $2x10^{11}$ particle units group included 2/10 subjects reporting fever (1 was of grade 3), 3 presenting transient asymptomatic neutropenia or leukopenia and 2 presenting asymptomatic prolonged aPTT (consistent with an in-vitro effect on the laboratory assay). No safety concerns were identified by the investigators at the highest dose in this phase 1 study. A dose-dependent immune response was demonstrated at weeks 2 and 4.

On-going studies include a monovalent phase 1 study (n=60) in the United Kingdom (EBL01), a phase 1 study (n=91); in Mali (CVD-1000), a bivalent 2-dose study (n=100+10 with booster dose); a monovalent phase 2a

une consultation avec les experts des pays mettant en œuvre la vaccination pour approfondir ce qui peut (ou ne peut pas) être identifié et correctement étudié.

Le GACVS a également souligné que, comme pour l'introduction d'autres vaccins, il est essentiel de permettre la notification spontanée de tout problème d'innocuité lié à ce vaccin. Cela voudra dire de revoir les systèmes existants de surveillance de la sécurité vaccinale et de planifier des développements pour les améliorer à partir des outils disponibles et s'assurer des connaissances de ceux qui participent à la vaccination antipaludique. Cela implique aussi pour ces pays d'avoir mis en place des capacités suffisantes pour enquêter sur les cas d'événements indésirables graves et d'avoir accès à des experts pour évaluer le lien de cause à effet entre ces événements et l'administration du vaccin.

Innocuité des vaccins contre le virus Ebola

L'OMS soutient activement la coordination dans la mise au point d'un vaccin et y joue un rôle essentiel. Deux vaccins contre le virus Ebola sont actuellement en phase 1 des essais cliniques: le ChAd3-EBO-Z (GSK Biologicals/NIAID) et le rVSV-ZEBOV (NewLink/Merck). Les calendriers pour la mise à disposition des données de la phase 1 et les grandes étapes des essais en phase 2/3 ont été présentés. Les essais en phase 3 devraient commencer au début de l'année 2015, avec des données initiales sur l'innocuité peut-être disponibles dès juin 2015. Malgré la nécessité d'un programme accéléré de mise au point du vaccin, les étapes cruciales pour en garantir l'innocuité et la qualité sont respectées. Des comités des bonnes pratiques de fabrication surveillent la qualité. Des comités d'éthique, des conseils de surveillance des données sur l'innocuité et d'autres conseils scientifiques supervisent l'ensemble des essais et s'intéressent en particulier au besoin d'obtenir des données de grande qualité.

1) Le vaccin ChAd3-EBO-Z se compose d'un vecteur recombinant dérivé d'un adénovirus de chimpanzé de type 3 (ChAd3) à réplication défectueuse codant la glycoprotéine du virus Ebola Zaïre (EBOV-Z). Les données précliniques ont révélé une immunité aiguë contre le virus EBOV-Z après une seule dose et une immunité durable après une séquence dite «prime-boost» (primovaccination-rappel). Les résultats ont été présentés pour l'essai VRC 207 en phase 1 (site: États-Unis; produit: bivalent 2×10^{10} et 2×10^{11} particules; phase 1; n = 20; date de début: 2 septembre 2014).[7] Les données sur l'innocuité et la réactogénicité dans le groupe de 2×10^{11} particules ont comporté 2 sujets sur 10 signalant de la fièvre (1 de degré 3), 3 présentant une neutropénie ou une leucopénie asymptomatique transitoire et 2 présentant un allongement asymptomatique du temps de céphaline activé (conforme à un effet in vitro lors de l'essai en laboratoire). Les chercheurs n'ont constaté aucun problème d'innocuité à la dose la plus élevée au cours de cette étude en phase 1. Une réponse immunitaire dépendante de la dose a été mise en évidence aux semaines 2 et 4.

Les études en cours comportent une étude de dose monovalente en phase 1 (n = 60) au Royaume-Uni (EBL01), une étude en phase 1 (n = 91); au Mali (CVD-1000), une étude de 2 doses bivalentes (n = 100 + 10 avec dose de rappel); une étude de

[7] Ledgerwood et al. Chimpanzee adenovirus vector Ebola vaccine — Preliminary Report. NEJM 2014 e-pub 26 November

[7] Ledgerwood et al. Chimpanzee adenovirus vector Ebola vaccine – Preliminary Report. NEJM 2014 e-pub 26 novembre.

study (n=120) in Switzerland (Cad3-EBOZ Lau); and a monovalent study (n=20) in USA (VRC 207 part 2). Two phase 1 and 1a trials are planned in Mali and Uganda.

(2) The rVSV-ZEBOV vaccine is a recombinant vesicular stomatitis virus with the G protein of the VSV envelope deleted and replaced by the G protein of the EBOV-Z. As at 28 November 2014, a total of 69 subjects had received $3x10^6$ or $5x10^7$ particle units vaccine doses in several phase 1 trials in progress (Gabon, Germany, Kenya, Switzerland, USA – 2 sites). The reactogenicity profile was presented as being acceptable, without serious adverse events. Systemic adverse events at grade 1–2 have included fever, fatigue, myalgia, headache and transient decreased white blood cell counts. These were generally seen during the first 3 days post administration. The percentage of fever varied between study sites. There was minimal evidence of vaccine virus shedding.

Initial data have not elicited any major safety concerns with respect to either product. However, additional data are needed in order to assess any rare or delayed reactions as well as risk in particular population subgroups such as immune deficient individuals, pregnant women and patients with chronic medical conditions.

GACVS considered the role of various stakeholders in the development of Ebola virus vaccines, in particular agencies involved with the assessment of clinical trial data, the Strategic Advisory Group of experts on immunization (SAGE) for providing recommendations about vaccine use and implementation strategies, and GACVS for risk assessment. A GACVS subgroup will be set up in order to promptly address new evidence and assess risks related to Ebola virus vaccines.

Performance indicators for vaccine safety monitoring systems

Globally there is considerable variation in reporting rates for adverse events following immunization (AEFI) between countries and regions. Currently, a large number of countries report few or no AEFI. There are no globally accepted indicators which could demonstrate the functionality of an AEFI surveillance system. Establishing such indicators is an important element for assessing progress in the development of AEFI surveillance systems. The Global Vaccine Action Plan includes the establishment and strengthening of AEFI reporting as a priority activity for the strengthening of all immunization programmes. There is a need for at least one performance indicator for monitoring progress against that objective.

The intent of AEFI indicators is not to define standards whereby countries can be compared. It is acknowledged that individual countries are at different stages of maturity with regard to AEFI safety systems, that different systems are in place (including the use of different vaccine products) and that it is difficult to capture the complexity and functionality of a system with a single set of indicators. Thus, the primary purpose of the AEFI

dose monovalente en phase 2a (n = 120) en Suisse (Cad3-EBOZ Lau); et une étude de dose monovalente (n = 20) aux États-Unis (VRC 207, deuxième partie). Deux essais en phase 1 et 1a sont prévus au Mali et en Ouganda.

2) Le vaccin rVSV-ZEBOV est un virus recombinant de la stomatite vésiculaire dans lequel la protéine G de l'enveloppe du VSV est supprimée et remplacée par la protéine G du virus EBOV-Z. Au 28 novembre 2014, au total 69 sujets avaient reçu des doses vaccinales de 3×10^6 ou 5×10^7 particules dans le cadre de plusieurs essais en phase 1 en cours (Allemagne, États-Unis – 2 sites, Gabon, Kenya, Suisse). Le profil de réactogénicité a été présenté comme acceptable, sans événements indésirables graves. On a observé dans les événements indésirables généraux de degré 1-2 de la fièvre, de la fatigue, des myalgies, des céphalées et une baisse transitoire de la numération des leucocytes, en général au cours des 3 premiers jours suivant l'administration. Le pourcentage des cas de fièvre a été variable selon les sites d'étude. Il y a des signes minimaux d'excrétion de la souche vaccinale.

Les données initiales n'ont pas mis à jour de problèmes majeurs d'innocuité pour ces 2 produits. Il faudra en revanche obtenir des données supplémentaires pour évaluer des réactions rares ou retardées susceptibles de se produire, ainsi que les risques dans certains sous-groupes de la population, comme les sujets immunodéficients, les femmes enceintes et les patients souffrant d'affections médicales chroniques.

Le GACVS a étudié le rôle des diverses parties prenantes dans la mise au point des vaccins contre le virus Ebola, en particulier les organismes participant à l'évaluation des données des essais cliniques, le Groupe stratégique consultatif d'experts sur la vaccination (SAGE), pour donner des recommandations sur l'utilisation des vaccins et les stratégies de mise en œuvre, ainsi que du GACVS pour l'évaluation du risque. Ce dernier va établir un sous-groupe chargé de s'intéresser rapidement aux nouvelles données factuelles et d'évaluer les risques liés aux vaccins contre le virus Ebola.

Indicateurs de performance pour les systèmes de surveillance de la sécurité vaccinale

On observe à l'échelle mondiale de grandes variations dans les taux de notification des manifestations post-vaccinales indésirables (MAPI) entre les pays et les régions. Actuellement, un grand nombre de pays ne signalent que peu ou pas de MAPI. Il n'existe pas d'indicateurs mondialement reconnus qui pourraient démontrer la fonctionnalité d'un système de surveillance des MAPI. La création de tels indicateurs est un élément important pour évaluer les progrès dans l'élaboration des systèmes de surveillance des MAPI. Le Plan d'action mondial pour les vaccins inclut la mise en place et le développement de la notification des MAPI en tant qu'action prioritaire pour le renforcement de tous les programmes de vaccination. Il est nécessaire d'avoir au moins un indicateur de performance pour suivre les progrès en vue d'atteindre cet objectif.

La finalité des indicateurs des MAPI n'est pas de définir des normes à l'aune desquelles comparer les pays. Il est admis que les pays se trouvent à divers stade de maturité concernant les systèmes de surveillance, que différents systèmes sont en place (y compris avec l'utilisation de produits vaccinaux variés) et qu'il est difficile de saisir la complexité et le fonctionnement d'un système au moyen d'un seul ensemble d'indicateurs. Les indicateurs de la surveillance des MAPI ont donc pour principal

surveillance indicators will be to provide countries with standards for the evaluation of progress towards functional passive vaccine safety surveillance. The aim will be for all countries to achieve a minimal threshold of AEFI reporting and then to progressively attain one or more of the more advanced indicators. This will allow working targets to be set and to be progressively improved upon.

GACVS considered a number of principles in deriving a set of indicators for AEFI surveillance. Three types of indicators are proposed: (i) to monitor the volume of AEFI reports; (ii) to monitor the quality of those reports; and (iii) to monitor the quality of the response to serious AEFI.

The proposed approach is to establish one single general indicator, accompanied by a number of more advanced indicators. Criteria to define the general indicator are based on principles of simplicity and generalizability. It will assess data already collected by countries which are also reported through the WHO-UNICEF Joint Reporting Form (JRF). The proposed general indicator is the ratio of AEFI reports per 100 000 surviving infants per year.

Advanced indicators are developed with the recognition that countries (and at times regions from large countries) are at different stages of advancement in their AEFI surveillance systems. Countries will be recommended to select one or more advanced indicators and to progressively advance from low to higher levels. A country achieving the highest level of the advanced indicator is considered to have the most advanced AEFI surveillance system. GACVS is pursuing the development of those advanced indicators. This will include piloting testing in countries with different levels of development of their AEFI surveillance systems; when finalized these indicators will be made available through the WHO vaccine safety website.

Criteria for assessing websites with vaccine safety content

The Vaccine Safety Net (VSN), a GACVS initiative, was launched in 2004 in response to the growing number of websites providing misinformation related to vaccine safety. In light of the rapid growth of the internet throughout the past decade, and the development of multiple new information sharing technologies, GACVS deemed it important to review the current criteria for good information practices to ensure that they remain evidence-based, relevant, current and comprehensive.

The primary objective of the VSN is to improve global dissemination of web-based vaccine safety information that adheres to good information practices. In order to assess information on vaccines publicly available on the internet, GACVS developed 4 categories of criteria – based on credibility, content, accessibility and design – to which sites providing information on vaccine safety should adhere. WHO evaluates websites against these criteria and provides a list of resources in multiple languages.[8]

objectif de fournir aux pays des normes d'évaluation des progrès en vue d'une surveillance passive opérationnelle de la sécurité vaccinale. Pour tous les pays, le but sera de parvenir à un seuil minimal de notification des MAPI puis, progressivement, d'atteindre un ou plusieurs des indicateurs plus avancés. Cela permettra de fixer des cibles de travail puis, ensuite, de les améliorer progressivement.

Le GACVS a pris en compte un certain nombre de principes dans l'établissement d'un ensemble d'indicateurs pour la surveillance des MAPI. Trois types d'indicateurs sont proposés: i) surveiller le volume de rapports; ii) surveiller la qualité de ces rapports; et iii) surveiller la qualité de l'action en réponse aux MAPI graves.

L'approche proposée consiste à fixer un seul indicateur général, accompagné d'un certain nombre d'indicateurs plus perfectionnés. Les critères de définition de l'indicateur général reposent sur les principes de simplicité et de possibilité de le généraliser. Il évaluera les données déjà collectées par les pays et transmises au moyen du Formulaire conjoint de déclaration OMS/UNICEF. L'indicateur général proposé est le nombre de rapports de MAPI pour 100 000 nourrissons survivants par an.

Les indicateurs avancés sont élaborés en reconnaissant que les systèmes de surveillance des MAPI dans les pays (et parfois dans différentes régions des grands pays) en sont à des stades variables de développement. Il sera recommandé aux pays de sélectionner un ou plusieurs indicateurs avancés puis de passer progressivement aux niveaux supérieurs. On considère que, lorsqu'un pays a atteint le niveau le plus élevé d'un indicateur avancé, il a le système de surveillance des MAPI le plus perfectionné. Le GACVS travaille sur l'élaboration de ces indicateurs perfectionnés, ce qui inclura des essais pilotes dans des pays à différents stades de développement de leurs systèmes de surveillance des MAPI; une fois finalisés, ces indicateurs seront disponibles en ligne sur le site OMS de la sécurité mondiale des vaccins.

Critères d'évaluation des sites Internet ayant un contenu sur la sécurité des vaccins

Le Réseau pour la sécurité des vaccins (VSN), initiative du GACVS, a été lancé en 2004 en réponse au nombre croissant de sites en ligne donnant des informations trompeuses sur la sécurité des vaccins. Compte tenu du développement rapide d'Internet ces 10 dernières années et des multiples technologies nouvelles de partage de l'information, le GACVS a jugé qu'il était important de passer en revue les critères actuels pour les bonnes pratiques en matière d'information, afin de s'assurer qu'elles demeurent fondées sur des bases factuelles, pertinentes, actualisées et complètes.

Le Réseau VSN a pour objectif principal d'améliorer la diffusion mondiale sur le Web des données concernant la sécurité des vaccins en respectant les bonnes pratiques en matière d'information. Pour évaluer les renseignements en ligne auxquels le public a accès, le GACVS a défini 4 catégories de critères basés sur la crédibilité, le contenu, l'accessibilité et la présentation, que doivent respecter les sites fournissant des informations sur la sécurité des vaccins. L'OMS évalue les sites en fonction de ces critères et fournit une liste des ressources dans de multiples langues.[8]

[8] See WHO VSN webpage: http://www.who.int/vaccine_safety/initiative/communication/network/vaccine_safety_websites/en/

[8] Voir la page de l'OMS sur le réseau VSN: http://www.who.int/vaccine_safety/initiative/communication/network/vaccine_safety_websites/fr/.

A working group revisited the criteria between September and December 2014. Throughout the revision process, the working group focused on 6 key factors: (1) reducing and consolidating the criteria; (2) revisiting the wording for clarity/currency; (3) revisiting the categories of criteria; (4) determining feasibility of implementation by websites; (5) identifying crucial criteria that must be met before websites are permitted to join the VSN; and (6) recognition of emerging standards and trends such as mobile platforms and social networks.

The working group presented an update on the VSN and a draft set of revised criteria for consideration at the December 2014 GACVS meeting. The Committee reviewed each criterion; discussion and recommendations centered on issues of particular sensitivity, such as websites' transparency of sponsorship.

The working group will amend the draft revised criteria according to the recommendations from GACVS and prepare a final set of revised criteria to be presented to the GACVS in June 2015. The working group will also develop a detailed guidance document, as a supplement to the list of criteria, to provide website owners with detailed instructions and examples on how to meet each criterion. Once endorsed by GACVS, the revised criteria and the guidance document will be posted on the WHO VSN webpage.

With respect to additional next steps, the working group will conduct an analysis of communication trends and related platforms, provide a recommendation on whether the VSN should assess these new technologies, and determine whether good information practices already exist for these information platforms. The results of this analysis will inform the development of a 2-year strategic plan for the VSN. The working group will present both the proposal regarding adding new technologies to the VSN and the 2-year plan to the GACVS in June 2015.

Un groupe de travail a revu les critères entre septembre et décembre 2014. Tout au long du processus, il a axé la révision sur 6 facteurs essentiels: 1) diminution et regroupement des critères; 2) révision du libellé pour les besoins de clarté et d'actualisation; 3) révision des catégories; 4) détermination de la faisabilité de la mise en œuvre par les sites; 5) détermination des critères cruciaux à remplir avant de permettre aux sites en ligne de rejoindre le Réseau; 6) reconnaissances des normes et tendances émergentes, comme les plateformes mobiles et les réseaux sociaux.

Le groupe de travail a présenté une actualisation du Réseau et un projet de critères révisés à étudier lors de la réunion du GACVS en décembre 2014. Le Comité a passé en revue chaque critère, avec des discussions et des recommandations centrées sur des aspects particulièrement sensibles, comme la transparence du parrainage des sites.

Le groupe de travail amendera le projet de révision des critères en fonction des recommandations du GACVS et préparera un ensemble définitif de critères révisés à présenter au Comité en juin 2015. Il rédigera aussi un document détaillé d'orientation, en complément de la liste des critères, pour fournir aux propriétaires des sites des instructions détaillées et des exemples sur la façon de remplir chaque critère. Une fois approuvés par le GACVS, les critères révisés et le document d'orientation seront publiés en ligne sur la page OMS du Réseau.

Pour ce qui est des prochaines étapes, le groupe de travail fera une analyse des tendances de la communication et des plateformes qui y sont liées, fournira une recommandation indiquant si le Réseau doit évaluer ces nouvelles technologies et déterminera s'il existe déjà des bonnes pratiques en matière d'information sur ces plateformes. Les résultats de cette analyse orienteront l'élaboration d'un plan stratégique sur 2 ans pour le Réseau. Le groupe de travail présentera au GACVS en juin 2015 la proposition d'ajouter les nouvelles technologies au Réseau et le plan sur 2 ans.

Use of vaccines during pregnancy

With increased attention to the benefits of some vaccines administered to pregnant women there is also a need to better understand safety implications. GACVS noted the new work to harmonize case definitions for AEFI related to vaccination in pregnancy by an ad hoc voluntary group of experts, the Brighton Collaboration working jointly with WHO. The Committee welcomed the ongoing work to strengthen relevant research and communication in maternal immunization safety. The proposed activities build on previous successful work based on a stakeholder review, collation of currently used terms and definitions and a series of Brighton Collaboration working group meetings, to produce a set of definitions and application of terms for vaccine pharmacovigilance. GACVS identified the regulatory needs to map these definitions to MedDRA codes, the existence of case definitions already in use, for instance in pregnancy registers, and electronic health and vital statistics datasets. It is recognized that it will be challenging to reach a consensus and it will be difficult to apply these definitions in epidemiological studies in low- and middle-income settings given limited

Utilisation des vaccins pendant la grossesse

Avec l'attention accrue portée aux effets bénéfiques de certains vaccins administrés aux femmes enceintes, il est également nécessaire de mieux comprendre les conséquences au niveau de la sécurité. Le GACVS a pris note du nouveau travail visant à harmoniser les définitions de cas pour les MAPI liées à la vaccination pendant la grossesse et effectué par un groupe spécial d'experts volontaires, la Brighton Collaboration œuvrant conjointement avec l'OMS. Le Comité s'est félicité des travaux en cours pour renforcer les études et les communications intéressant la sécurité vaccinale chez la mère. Les activités proposées s'appuient sur des travaux antérieurs fructueux reposant sur un examen des parties intéressées, le rassemblement des termes et des définitions actuellement utilisés et un série de réunions du groupe de travail de la Brighton Collaboration, pour produire un ensemble de définitions et d'applications des termes pour la pharmacovigilance concernant les vaccins. Le GACVS a déterminé les besoins réglementaires pour inscrire ces définitions dans les codes MedDRA, l'existence de définitions de cas déjà utilisées, par exemple dans les registres des grossesses, et les bases de données électroniques sur la santé et les statistiques vitales. Il est admis qu'il sera difficile de parvenir à un consensus et d'appliquer ces définitions dans des études

resources and health capacity. Capacity-building for AEFI monitoring in low-income settings requires ongoing support and will facilitate the use of these case definitions. ■

épidémiologiques dans des contextes de revenu faible ou intermédiaire, compte tenu des ressources et des capacités sanitaires limitées. Le renforcement des capacités pour la surveillance des MAPI dans des contextes de faible revenu nécessitera un appui en continu et facilitera l'utilisation de ces définitions de cas. ■

WHO web sites on infectious diseases – Sites internet de l'OMS sur les maladies infectieuses

Avian influenza	**http://www.who.int/csr/disease/avian_influenza/en/**	Grippe aviaire
Buruli ulcer	**http://www.who.int/buruli/en/**	Ulcère de Buruli
Child and adolescent health and development	**http://www.who.int/child_adolescent_health/en/**	Santé et développement des enfants et des adolescents
Cholera	**http://www.who.int/cholera/en/**	Choléra
Deliberate use of biological and chemical agents	**http://www.who.int/csr/delibepidemics/informationresources/en/**	Usage délibéré d'agents chimiques et biologiques
Dengue (DengueNet)	**http://apps.who.int/globalatlas/**	Dengue (DengueNet)
Epidemic and pandemic surveillance and response	**http://www.who.int/csr/en/**	Alerte et action en cas d'épidémie et de pandémie
Eradication/elimination programmes	**http://www.who.int/infectious-disease-news/**	Programmes d'éradication/élimination
Filariasis	**http://www.filariasis.org**	Filariose
Geographical information systems (GIS)	**http://gamapserver.who.int/mapLibrary/**	Systèmes d'information géographique
Global atlas of infectious diseases	**http://apps.who.int/globalatlas/**	Atlas mondial des maladies infectieuses
Global Outbreak Alert and Response Network (GOARN)	**http://www.who.int/csr/outbreaknetwork/en/**	Réseau mondial d'alerte et d'action en cas d'épidémie (GOARN)
Health topics	**http://www.who.int/topics/en**	La santé de A à Z
Influenza	**http://www.who.int/csr/disease/influenza/en/**	Grippe
Influenza network (FluNet)	**http://who.int/flunet**	Réseau grippe (FluNet)
International Health Regulations	**http://www.who.int/ihr/en/**	Règlement sanitaire international
International travel and health	**http://www.who.int/ith/en/**	Voyages internationaux et santé
Intestinal parasites	**http://www.who.int/topics/intestinal_diseases_parasitic/en/**	Parasites intestinaux
Leishmaniasis	**http://www.who.int/leishmaniasis/en**	Leishmaniose
Leprosy	**http://www.who.int/lep/en**	Lèpre
Lymphatic filariasis	**http://www.who.int/lymphatic_filariasis/en/**	Filiariose lymphatique
Malaria	**http://www.who.int/malaria/en**	Paludisme
Neglected tropical diseases	**http://www.who.int/neglected_diseases/en/**	Maladies tropicales négligées
Outbreak news	**http://www.who.int/csr/don/en**	Flambées d'épidémies
Poliomyelitis	**http://www.polioeradication.org/casecount.asp**	Poliomyélite
Rabies network (RABNET)	**http://www.who.int/rabies/en**	Réseau rage (RABNET)
Report on infectious diseases	**http://www.who.int/infectious-disease-report/**	Rapport sur les maladies infectieuses
Global Foodborne Infections Network (GFN)	**http://www.who.int/gfn/en**	Réseau mondial d'infections d'origine alimentaire
Smallpox	**http://www.who.int/csr/disease/smallpox/en**	Variole
Schistosomiasis	**http://www.who.int/schistosomiasis/en/**	Schistosomiase
Tropical disease research	**http://www.who.int/tdr/**	Recherche sur les maladies tropicales
Tuberculosis	**http://www.who.int/tb/en** and/et **http://www.stoptb.org**	Tuberculose
Immunization, Vaccines and Biologicals	**http://www.who.int/immunization/en/**	Vaccination, Vaccins et Biologiques
Weekly Epidemiological Record	**http://www.who.int/wer/**	Relevé épidémiologique hebdomadaire
WHO Lyon Office for National Epidemic Preparedness and Response	**http://www.who.int/ihr/lyon/en/index.html**	Bureau OMS de Lyon pour la préparation et la réponse des pays aux épidémies
WHO Pesticide Evaluation Scheme (WHOPES)	**http://www.who.int/whopes/en**	Schéma OMS d'évaluation des pesticides (WHOPES)
WHO Mediterranean Centre for Vulnerability Reduction, Tunis	**http://wmc.who.int/**	Centre Méditerranéen de l'OMS pour la Réduction de la Vulnérabilité à Tunis (WMC)
Yellow fever	**http://www.who.int/csr/disease/yellowfev/en/**	Fièvre jaune

SAGE Polio Working Group

Thursday, 19 February 2015

Conference Call Notes

INTRODUCTION

A SAGE Polio Working Group (WG) teleconference was held on 19 February 2015 to discuss persistent cVPDV2 transmission in relation to the OPV2 withdrawal "trigger," and the process of verification of poliovirus containment in essential facilities. The call was attended by the following WG members: Peter Figueroa (Chair), Walter Orenstein, Walter Dowdle, T Jacob John, Elizabeth Miller, Kimberly Thompson, Hyam Bashour, Antoine Kabore, and Francis Nkrumah. Nick Grassly, Zulfiqar Bhutta and Yagob Al-Mazrou were unable to attend.

This note presents a summary of the presentations, key discussion points, decisions and recommendations from the call.

OBJECTIVES

The objectives of the meeting were to:

1. Review the current status of persistent cVDPV2 transmission in Nigeria and Pakistan and mitigation approaches in each country. (**Information**)
2. Endorse a proposal for contingency actions that would enable OPV2 withdrawal on the planned date of April 2016, in the event that persistent cVDPV2 continues to circulate after March 2015. (**Decision**)
3. Endorse a proposal for the verification process of poliovirus containment in essential facilities (**Decision**)

PRESENTATIONS, DISCUSSIONS AND CONCLUSIONS

TOPIC 1 **Current situation of persistent cVDPV2 in Nigeria and Pakistan (Information)**
In 2014, persistent cVDPV2 transmission was identified in only Nigeria and Pakistan. Overall, incidence of cVDPV2 decreased in the second half of 2014 following tOPV/IPV campaigns in affected areas, although AFP cases caused by cVDPV2 viruses occurred with onset as late as November 2014 in Nigeria and December 2014 in Pakistan. In Nigeria, two lineages of persistent cVDPV2 circulated in 2014, but cVDPV2 detection declined in Borno, Sokoto and Kano states following two rounds of large-scale tOPV SNIDs in northern Nigeria starting in mid-2014 supplemented with targeted tOPV+IPV campaigns in Borno and parts of Yobe. cVDPV2-related AFP cases or cVDPV2-positive environmental surveillance (ES) samples have not been identified since the most recent tOPV SNID conducted in November 2014. To ensure that current persistent cVDPV2 transmission is interrupted within the first half of 2015, Nigeria is planning an aggressive programme of tOPV SIAs and targeted mop-up campaigns. Two tOPV SIAs are planned for March (NID) and April (SNID), with IPV added in selected high-risk areas. In Pakistan, two persistent cVDPV2 lineages stopped circulating during the first half of 2014. A new persistent lineage emerged in Gadap, Karachi, in July 2014, and continued to circulate as of January 2015. Pakistan will implement 4 tOPV campaigns during the first half of 2015 in the areas affected by persistent cVDPV2 in 2014, 1 in March (NID), 1 in April (SNID), and 2 in May (SNIDs), with IPV added in selected highest-risk areas.

TOPIC 2 **Contingency plan to monitor and stop cVDPV2 in advance of OPV2 withdrawal (Decision)**
For Decision: **Context:** Contingency actions to interrupt persistent cVDPV2 transmission during the second half of 2015 to ensure global withdrawal of OPV2 in April 2016 remains on track. *After reviewing the progress and the contingency plans for cessation of persistent cVDPV2 in Pakistan and Nigeria in 2015, does the WG agree to review the epidemiology of persistent cVDPV2 in June and again in September 2015 in the event that persistent cVDPV2 continues to circulate after March 2015, to facilitate the final SAGE endorsement of OPV2 withdrawal date of April 2016?* Epidemiology: Transmission of all persistent cVDPV2 lineages circulating in Nigeria and Pakistan at the beginning of 2014 declined substantially, although a new lineage was confirmed in Pakistan in January 2015 indicating persistent programmatic failures that could delay planned OPV2 withdrawal.

Confidence in surveillance: Both Nigeria and Pakistan have maintained surveillance indicators (i.e., non-polio AFP rate and % stool adequacy) at international standards during the past 12 months, although with some sub-national heterogeneity largely related to insecurity (Borno, FATA, Karachi). Importantly, Nigeria expanded its environmental surveillance sites to 34 in 2014 with plans to improve sensitivity further (particularly with respect to sampling frequency), and has started contact-sampling of all AFP cases in Borno and Yobe states. In addition, Nigeria has been conducting sero-prevalence surveys in high-risk states to monitor serotype-specific immunity children under age 5 years in order to assess progress and target immunization activities.

Pakistan expanded its environmental surveillance sites to 36, with a number of new sites becoming functional in late 2014. Pakistan will start conducting sero-prevalence surveys in 2015.

Confidence in SIA quality and regimen: Multiple tOPV campaigns (some with IPV co-administration in highest risk areas) were conducted during the second half of 2014, with evidence from lot quality assurance sampling (LQAS) of improving quality of rounds, particularly in Nigeria, and improved access to inaccessible populations in Pakistan. Both countries have co-administered IPV in campaigns to vaccinate specific high-risk populations. Both countries have established plans for multiple tOPV campaigns in the first half of 2015 and the SIA plan for the second half of 2015, which will be finalized in April, will also include additional tOPV SIAs to ensure interruption of any residual cVDPV2 transmission and prevention of the development of future cVDPVs. The SAGE endorsed the GPEI approach for using a risk-based tOPV SIA regimen to reduce the risk of new cVDPV2 emergence at its October 2014 meeting.

Country readiness for OPV2 withdrawal: Countries continue to make progress towards achieving the 5 readiness criteria recommended by the WG. The SAGE concluded in October 2014 that global preparations were on track for OPV2 withdrawal in April 2016, and recommended that Member States accelerate their preparations.

In its 136th session, the Executive Board of WHO decided to call on Member States to ensure global readiness by the end of 2015 for the coordinated withdrawal of oral poliovirus vaccines containing the type 2 component and directed the Secretariat to draft a resolution for submission to the World Health Assembly scheduled in May 2015.

The WG discussed the GPEI's capacity to ensure the absence of persistent cVDPV2 preceding OPV2 withdrawal in April 2016. The WG was encouraged by progress made in Nigeria and Pakistan, including the expansion of environmental surveillance and the specific efforts to interrupt persistent cVDPV2 transmission with tOPV and tOPV+IPV campaigns during the second half of 2014 in line with SAGE recommendations. The WG was also encouraged by the plans for multiple tOPV SIAs planned for the first half of 2015 in Nigeria and Pakistan, the opportunity to conduct additional tOPV campaigns in the second half of 2015, and the plan endorsed by SAGE to include multiple tOPV campaigns in the SIA calendar in the months preceding the switch.

Decision and Recommendations: *The WG agreed to review the epidemiology of persistent cVDPV2 in June and again in September 2015 in the event that persistent cVDPV2 continues to circulate after March 2015, to facilitate the final SAGE endorsement of OPV2 withdrawal date of April 2016. The WG made the following recommendations:*

1. *The program should maintain the target of April 2016 for OPV2 withdrawal.*
2. *Nigeria and Pakistan should ensure sufficient numbers of high quality tOPV or tOPV+IPV SIAs and mop-ups during the first half of 2015 to interrupt any ongoing persistent cVDPV2 transmission.*
3. *A teleconference should be held in June 2015 and either a teleconference or a face-to-face meeting should be held in September 2015.*

TOPIC 3
Verification of essential facilities' compliance with GAP III (Decision)

For Decision: *Does the WG endorse the approach proposed below for certification and verification of containment of polioviruses in essential facilities?*

Proposal: *Essential facilities implement GAPIII, and National Regulatory Authorities for containment (NRAcs) certify facilities against GAPIII and submit certification reports to Regional Certification Commissions (RCCs). In support of this process, RCCs may request that WHO verify the compliance of certified facilities against GAPIII, and countries or concerned facilities may also request WHO's verification in advance of RCC evaluation.*

NRAcs and WHO will use GAPIII as the basis to verify that essential facilities meet GAPIII requirements. Verification reports will be shared with all concerned stakeholders (e.g., facilities, NRAs and WHO). Responses to verification reports will be 3-fold:

- Facilities will address any non-compliance within an agreed timeframe, including follow-up and additional visits,

if necessary.

- NRAs will undertake an informed decision to revoke or maintain certification against GAPIII.
- RCC will undertake an informed decision as to whether the facility complies with GAPIII.

The WG discussed the verification process and was encouraged by the plan for GAPIII training for national regulatory bodies responsible for assessment and certification of facilities.

Decision and Recommendation: *The WG agreed to the proposed approach to containment verification and made the following recommendation:*

- *Data on progress towards implementation timelines should be provided to evaluate readiness to contain type 2.*

SAGE Polio Working Group
Thursday, 13 March 2015
Conference Call Notes

INTRODUCTION

A SAGE Polio Working Group (WG) teleconference was held on 13 March 2015 to review and endorse the programme approach to detection and response to cVDPV2 after March 2015, and to review the preparations for OPV2 withdrawal in April 2016.

The following WG members were in attendance: Peter Figueroa (Chair), Hyam Bashour, Walter Dowdle, Nick Grassly, Antoine Kabore, Yagob Al-Mazrou, Elizabeth Miller, and Kimberly Thompson. Zulfiqar Bhutta, T Jacob John, Francis Nkrumah, and Walt Orenstein were unable to attend.

This note provides a summary of the presentations, key discussion points, decisions and recommendations from the call.

OBJECTIVES

The objectives of the meeting were to:

1. Review "what-if" scenarios of cVDPV2 detection, during the period from April 2015 to March 2016, and endorse the proposed response plans together with the updated calendar for planned tOPV campaigns prior to OPV2 withdrawal **(Decision)**
2. Recognizing the recent progress in Nigeria and Pakistan, consider whether the deadline of end March 2015 for elimination of persistent cVDPV should no longer be applied as a 'trigger' for the SAGE to confirm April 2016 as the date for withdrawal of type 2 oral poliovirus vaccine, and whether instead, the WG would thoroughly assess progress in September 2015 and then advise SAGE on confirming the appropriate date for OPV2 withdrawal **(Decision)**
3. Review progress toward IPV introduction and preparations for OPV2 withdrawal (**Information**)

PRESENTATIONS, DISCUSSIONS AND RECOMMENDATIONS

TOPIC 1
cVDPV2 detection and response scenarios after March 2015 and proposal to no longer apply the deadline of end March 2015 as a 'trigger' for OPV2 withdrawal

Context: Following the 19 February 2015 SAGE Polio WG agreement to review the epidemiology of persistent cVDPV2 in June and September 2015 if persistent cVDPV2 is detected beyond March 2015, and further to program request to no longer apply the deadline of end March 2015 as a 'trigger' date for OPV2 withdrawal, the WG requested the development of scenarios for detection and response to cVDPV2 during the period of April 2015 to March 2016.

Update: epidemiology of persistent cVDPV2 in Pakistan and Nigeria
There has been no further detection of persistent cVDPV2 through AFP or environmental surveillance in Pakistan or Nigeria since the 19 February SAGE WG call. No persistent cVDPV2 strains have been detected in Nigeria since November 2014. The two persistent cVDPV2 strains that had emerged during 2012 in Pakistan have not been detected since June 2014 and the new cVDPV2 strain that emerged in July 2014 was last detected through environmental surveillance in January 2015.

cVDPV2 detection and response scenarios in Pakistan and Nigeria
Detection and response to persistent cVDPV2 scenarios were presented on Nigeria and Pakistan for the periods before (April-September 2015) and after (November 2015-March 2016) the October 2015 meeting at which SAGE is expected to confirm April 2016 as the date for all OPV-using countries to withdraw the type 2 oral poliovirus vaccine. If persistent cVDPV2 is detected during April-September 2015, in addition to full

implementation of all planned tOPV campaigns, the response will include the addition of intensified mopping-up tOPV campaigns and addition of tOPV and IPV campaigns as appropriate.

Recent epidemiology of cVDPV2 and detection and response scenarios in countries other than Nigeria and Pakistan ("other countries")

To provide a broader context of the outcome of cVDPV2 outbreaks and the impact of GPEI response activities, the epidemiology of cVDPV2 outbreaks during 2010-2015 to date was presented for countries other than Nigeria and Pakistan ("other countries").

There were 15 cVDPV2 events[1] during 2010-2015, with 84 reported cases in 9 "other countries."2 The median outbreak duration was 1.2 months (range: 0-32.2 months). The majority (13/15 or 87%) lasted <6 months, i.e., below the threshold used by the programme to define 'persistent transmission'. Regarding the origin of the outbreaks, 7/15 (47%) were new emergences and 8/15 (53%) were importations (4 from Nigeria, 1 from Chad, 1 from Somalia, and 2 from Pakistan). The size of the outbreaks involved primarily multiple-case events, 10/15 (66%) involving between 2-26 cases; however, there were 5/15 (33%) single-case events, 4 of which were importations from Nigeria.

Of the 15 cVDPV2 events, 73% were stopped by 2 or fewer campaigns and 87% were stopped by 4 or fewer campaigns: 7 (47%) stopped spontaneously; 2 (13%) after 1 SIA; 2 (13%) after 2 SIAs; 1 (7%) after 3 SIAs; and 2 (13%) after 4 SIAs. Only 1 (7%) outbreak (in Afghanistan) required 9 SIAs to stop the outbreak country-wide.

Based on the experience with cVDPV2 events in the past five years and anticipating the withdrawal of type 2 OPV in April 2016, scenarios in other countries on detection and response to VDPV2 were presented for the periods before (April-September 2015) and after (November 2015-March 2016) the October 2015 SAGE meeting. A risk-based approach was proposed that incorporated risk tiers for VDPV2 emergence and spread (Tier 1 vs. Tier 2-4 countries) and type of VDPV2 detected (cVDPV2 or aVDPV2) and proximity to the date of OPV2 withdrawal. The most intensive mopping up response would be implemented in the highest risk category scenario which would be the detection of cVDPV2 in a Tier 1 country during the October 2015-March 2016 timeframe. Based on the updated tOPV SIA calendar for preventative campaigns (which is described below) and this risk-based strategy, as we approach the OPV2 withdrawal date, a progressively intensified response would be undertaken following detection of any VDPV2.

Updated tOPV SIA calendar to mitigate the risk of new cVDPV2 emergence after OPV2 withdrawal

A tOPV SIA calendar for the period July 2015 through March 2016 was updated. The three main objectives of the SIA strategy were to: 1) to interrupt WPV1 transmission in endemic and outbreak countries; stop transmission of persistent cVDPV2; and increase population immunity to type 2 poliovirus in high-risk areas prior to the global withdrawal of OPV2.

The tOPV schedule to reduce the risk of cVDPV2 emergence was developed based on the cVDPV2 risk modelling approach that was endorsed by SAGE in October 2014. Additional SIA activities amounting to delivery of an additional 52 million tOPV doses have been added to the calendar reviewed by SAGE in October 2014.

Decisions:

1. *The WG endorsed the cVDPV2 detection and response strategies in Nigeria and Pakistan and the risk-based VDPV2 response strategy in other countries.*

2. *The WG also endorsed the tOPV SIA schedule to reduce the risk of cVDPV2 emergence. The WG made the following recommendations:*
    a. *The WG should be updated on the tOPV supply situation in June 2015;*
    b. *The program should ensure high coverage (e.g. ≥80%) is achieved, especially in areas with low levels of immunity to type 2 poliovirus and where only a single tOPV SIA round is planned within 6*

[1] NB: data was updated following the call – the updated data has been included here to align with the background document on cVDPV2 epidemiology that has been developed for the SAGE meeting.

[2] Afghanistan, Cameroon, Chad, China, DRC, Kenya, Niger, South Sudan and Yemen

months of OPV2 withdrawal.

3. *The WG agreed to review the epidemiology of persistent cVDPV2 in June and in greater detail during its meeting in September 2015 with the objective to ensure that the elimination of persistent cVDPV2 is on track before OPV2 withdrawal in April 2016. The WG made the following recommendations :*
    a. *The previous deadline of March 2015 for elimination of persistent cVDPV2 as a "trigger" for OPV2 withdrawal will no longer be applied. Instead, the final recommendations by the WG to SAGE will be given after the WG meeting in September 2015 and will be based upon whether or not there is clear evidence of progress in the two countries with persistent cVDPVs that would provide a high degree of confidence in October 2015 that by the time of the switch the criteria for elimination of persistent cVDPV2 circulation will be met.*
    b. *Given the serious implications of delay for all countries involved in OPV2 withdrawal, the WG agreed that once SAGE confirms April 2016 as the date for withdrawal of type 2 OPV, the switch should proceed as planned. Contingency strategies to respond to detection of any persistent cVDPV2 subsequent to the October decision will be submitted by GPEI to the WG for review at its June meeting, including the scenario of new cVDPV detection just prior to the scheduled switch.*

The Chair also requested WG members to share with the WG and secretariat any other "what if" scenarios that we have not considered so that the June conference call can be thoroughly prepared well in advance.

TOPIC 2
Update on preparation for OPV2 withdrawal (Information)

The WG reviewed the update on the plans and preparations for OPV2 withdrawal, especially global IPV supply and bOPV licensure, and commended the progress made in the preparations.

Update on global IPV supply

There are currently 126 tOPV-only using countries that plan to introduce at least one dose of IPV by the end of 2015.

The current global supply of IPV is limited mainly to 2 manufacturers (Sanofi and BBio), both of whom have indicated that they will not be able to meet their initial supply commitments. This will result in a deficit of 8 million IPV doses by BBio alone. Furthermore, an additional 1.5 million doses of IPV has been requested for SIAs in Pakistan and Nigeria. The constraints on supply due to the additional doses requested will result in the delay of IPV introduction in Tier 3 and 4 countries to Q4 2015. Despite the delay in these countries, more than 80% of the global birth cohort (in 104 countries) will be covered with IPV by the end of 2015, including all Tier 1 and Tier 2 countries.

Update on bOPV licensure

There are 156 tOPV-using countries and territories that need to switch from tOPV to bOPV. The current label for bOPV restricts its use to SIAs. The modification of indication (label change) for bOPV by manufacturers, for its use in routine immunization schedules, is forecast for completion by mid-2015, with anticipated licensure by the end of 2015. Work is currently underway to facilitate the process by which, as an interim measure, WHO member states accept bOPV for routine immunization based on WHO prequalification.

Recommendations: *The WG made the following recommendation:*

- The WG should be updated in June 2015 on the contingency plan for tOPV supply during 2016 in case of postponement of OPV2 withdrawal to 2017.

Persistent circulating vaccine-derived poliovirus type 2 (cVDPV2) - current status in preparation of the tOPV to bOPV switch

Background paper for the meeting of SAGE, April 14-16, 2015

1 Introduction and background

Since the first outbreak due to a vaccine-derived poliovirus (VDPV) in 2000 on the island of Hispaniola,[1] it has become clear that live oral polio vaccine (OPV) viruses can, on rare occasion, circulate in communities and accumulate sufficient mutations to regain transmissibility and neurovirulence similar to wild-type polioviruses (circulating vaccine-derived polioviruses [cVDPVs]).[2] While VDPV outbreaks associated with each of the three components of trivalent OPV (tOPV) have been reported, from 2000-2015 the vast majority of VDPV outbreaks (97%) and related cases (>90%) have been associated with the type 2 component of OPV (OPV2).[3] In addition, OPV2 is estimated to cause up to 40% of vaccine-associated paralytic polio (VAPP) cases.[4]

Since November 2012, all cases of polio related to wild virus have been type 1. Wild poliovirus type 2 (WPV2) has not been detected globally since October 1999, when the last case was reported from Aligarh, India.[5] Therefore, at this point in the polio eradication effort, all type 2 polio cases are associated with the type 2 component of OPV. In order to manage the risks associated with the continued use of OPV,[6] the 'endgame strategy' of the Global Polio Eradication Initiative (GPEI), as outlined in the 2013-2018 GPEI Strategic Plan,[7] calls for the sequential withdrawal of OPV strains, starting with the withdrawal of OPV2 through a globally synchronized switch from tOPV to bOPV.[8] To reduce the risk associated with OPV2 withdrawal, in November 2013 SAGE endorsed five readiness criteria,[i] as well as the global absence for at least 6 months of all persistent type 2 cVDPVs (cVDPV2).[9]

In April 2014, SAGE emphasized that the elimination of cVDPV2 must be a high priority for the polio eradication effort to remain on-track to achieve the major milestones of the 'endgame plan,' including the withdrawal of type 2 component of tOPV by April 2016.[10] This background paper provides an update on the current status of persistent cVDPV2 transmission in Nigeria and Pakistan and information on VDPV2 outbreaks in other countries from 2010-2015; discusses immunization activities conducted and planned to interrupt currently persistent cVDPV2 transmission; and introduces detection and response scenarios for any new emergences of VDPV2.

2 Current status of persistent cVDPV2 transmission in Nigeria and Pakistan

Since 2005, 15 countries reported episodes of cVDPV2. However, since 2010, persistent cVDPV2 transmission (i.e., longer than 6 months after detection) has occurred in only 4 countries: Nigeria, Pakistan, Chad and Afghanistan. In Chad and Afghanistan, persistent cVDPV2 transmission has not occurred since 2012 and 2013, respectively. Persistent cVDPV2 transmission was detected only in Nigeria and Pakistan in 2014.[11]

[i] (1) at least 1 dose of IPV included in the routine immunization programme in OPV-using countries; (2) bivalent oral polio vaccine (bOPV) licensed for routine immunization; (3) type 2 poliovirus surveillance and response protocols and monovalent OPV (mOPV) stockpile; (4) appropriate containment and handling of residual type 2 materials; and (5) verification of global eradication of wild poliovirus type 2.

2.1 Nigeria

Since 2005, more than 20 distinct emergences of cVDPV2 have been detected in Nigeria,[12,13] including seven that established persistent circulation. These cVDPV2 outbreaks were restricted to the northern states, where immunization coverage with tOPV was low and SIAs using tOPV were infrequent. Repeated seroprevalence surveys conducted in Sokoto and Kano states indicated that population immunity to type 2 was low and had dropped significantly in Kano state between 2011 and 2013.[14] Of the 20 emergences, only one lineage continued to circulate in 2014 in the northern states (see 'Nigeria Old' virus grouping, Figure 1) along with a cVDPV2 strain that was imported into northeastern Nigeria from Chad in 2011/2012 (see 'Nigeria-Chad' virus grouping, Figure 1). In 2014, 30 cVDPV2 polio cases were reported from Nigeria, compared to only 6 wild poliovirus type 1 (WPV1) cases. However, cVDPV2-related AFP cases or cVDPV2-positive environmental surveillance (ES) samples have not been identified since the most recent tOPV SNID conducted in November 2014.

From 2012 to mid-2014, the majority of SIAs conducted in Nigeria used bOPV to target remaining chains of WPV1 transmission – few tOPV campaigns were conducted. In each of 2012 and 2013, only one large-scale tOPV SIA was conducted in northern Nigeria. Moreover, vaccination efforts have been compromised due to insecurity and limited access in some critical areas, particularly in the northeastern states of Borno and Yobe. Since June 2014, IPV + tOPV campaigns have targeted high risk areas of Borno (June), Yobe (June) and Kano (November) states, and large-scale tOPV SIAs (SNIDs) were conducted in the northern states in August and November. For 2015, the Expert Review Committee on polio eradication in Nigeria has recommended an aggressive mopping-up response strategy to ensure that current persistent cVDPV2 transmission is interrupted within the first half of 2015. Two tOPV SIAs are planned for March (NID) and April (SNID), with IPV added in selected high-risk areas. Nigeria is planning to conduct additional immunization activities using IPV in April to address any areas of persistent virus circulation and ensure transmission is stopped, including raising immunity in internally displaced populations in Borno, Adamawa, Gombe, Nasarawa, Benue and Taraba; and raising immunity in other high-risk areas of northern states (including Kaduna and Sokoto). In addition, SIA plans in Nigeria include three tOPV SNIDs (July and October 2015, and January 2016) and two tOPV NIDs immediately before (February and March 2016) the planned OPV2 withdrawal.

2.2 Pakistan

Since mid-2012, there have been five distinct emergences of cVDPV2 in Pakistan. In 2014, two “old” lineages of cVDPV2 circulated causing 21 cases (compared to 306 WPV1 cases reported during the same year), with the majority of cases detected in the Federally Administered Tribal Areas (FATA) and adjacent districts of Khyber Pukhtunkhwa (KP) province, where insecurity and vaccination ban compromised access to children during SIAs. These two lineages have not been detected since June 2014. A new persistent lineage emerged in Gadaap, Karachi, in July 2014 and was last detected in January 2015 in an environmental surveillance sample.

Since mid-2014, there has been significant progress in vaccinating children displaced from inaccessible areas at transit vaccination posts, or through vaccination of internally displaced families in their accessible host communities. Two large tOPV SIAs were conducted in July (NID) and August (SNID) and small targeted campaigns with IPV were conducted between November 2014 and February 2015 in high-risk areas of Quetta, Killa Abdullah and Pishin districts (Balochistan province), FR Bannu (KP province) and high risk areas of Karachi (Sindh province). Pakistan will implement four tOPV campaigns during the first half of 2015 in areas

affected by persistent cVDPV2 in 2014: one in March (NID), one in April (SNID), and two in May (SNIDs), using tOPV + IPV in selected highest-risk areas. In addition, the SIA plan in Pakistan includes two tOPV SIAs (September and November 2015) and two tOPV SIAs immediately before (February and March 2016) the planned OPV2 withdrawal.

2.3 Pre-switch scenarios for cVDPV2 response in Pakistan and Nigeria

In October 2014, SAGE re-emphasized its previous recommendation that, in order to maintain the planned timeline towards the tOPV-bOPV switch in April 2016, the elimination of persistent cVDPV2 should have the same priority for the GPEI as the elimination of wild polioviruses.[15] To reduce the risk of cVDPV2 emergence after withdrawal of OPV2, SAGE endorsed a risk-based approach for boosting population immunity to type 2 polioviruses prior to OPV2 withdrawal. The strategy ensures that sufficient tOPV SIAs are planned and conducted in areas at highest risk of cVDPV2 emergence.

The October 2015 meeting SAGE is expected to confirm April 2016 as the date for all OPV-using countries to withdraw OPV2. In April 2015, SAGE will review progress toward IPV introduction, OPV2 withdrawal, bOPV licensure and progress towards elimination of persistent cVDPV2. Prior to the April 2015 meeting, the SAGE Polio Working Group reviewed proposed scenarios of detection and response to persistent and emerging cVDPV2 in Nigeria and Pakistan for the periods before (April - September 2015) and after (November 2015 - March 2016) the October 2015 SAGE meeting.

Given the high risk in these countries, if persistent cVDPV2 is detected during April-September 2015 the response will include ensuring full implementation of all planned tOPV campaigns, the addition of intense mopping-up campaigns, addition of IPV to tOPV campaigns in specific areas, and further intensification/frequency of activities as needed. The SAGE WG agreed to review the epidemiology of persistent cVDPV2 in June 2015 and in greater detail during its meeting in September 2015. The final recommendations by the WG to SAGE will be given after the WG meeting in September 2015 and will be based upon whether or not there is clear evidence of progress in the two countries with persistent cVDPVs that would provide a high degree of confidence in October 2015 that by the time of the switch the criteria for elimination of persistent cVDPV2 circulation will be met. Detection of cVDPV2 following the October 2015 SAGE meeting will activate further escalation of tOPV/tOPV+IPV mopping-up in addition to planned tOPV campaigns.

3 cVDPV2 epidemiology and response in "other countries"

To provide a broader context of the outcome of cVDPV2 emergence and outbreaks and of the impact of GPEI response activities, the following is a brief description of the epidemiology and duration of cVDPV2 outbreaks during 2010-2015 in countries other than Nigeria and Pakistan ("other countries").

There were 15 cVDPV2 events during 2010-2015, with 84 reported cases in 9 "other countries."[ii] The median outbreak duration was 1.2 months (range: 0-32.2 months). The majority (13/15 or 87%) lasted <6 months, i.e., below the threshold used by the programme to define 'persistent transmission'. Regarding the origin of the outbreaks, 7/15 (47%) were new emergences and 8/15 (53%) were importations (4 from Nigeria, 1 from Chad, 1 from Somalia, and 2 from Pakistan). The size of the outbreaks involved primarily multiple-case

[ii] Afghanistan, Cameroon, Chad, China, DRC, Kenya, Niger, South Sudan and Yemen

events, 10/15 (66%) involving between 2-26 cases; however, there were 5/15 (33%) single-case events, 4 of which were importations from Nigeria.

Of the 15 cVDPV2 events, 73% were stopped by 2 or fewer campaigns and 87% were stopped by 4 or fewer campaigns: 7 (47%) stopped spontaneously; 2 (13%) after 1 SIA; 2 (13%) after 2 SIAs; 1 (7%) after 3 SIAs; and 2 (13%) after 4 SIAs. Only 1 (7%) outbreak (in Afghanistan) required 9 SIAs to stop the outbreak country-wide.

Based on the experience with cVDPV2 events in the past five years and anticipating the withdrawal of type 2 OPV in April 2016, scenarios in other countries for detection and response to VDPV2 were presented for the periods before (April-September 2015) and after (November 2015-March 2016) the October 2015 SAGE meeting. A risk-based approach was proposed that incorporated risk tiers for VDPV2 emergence and spread (Tier 1 vs. Tier 2-4 countries) and type of VDPV2 detected (cVDPV2 or aVDPV2) and proximity to the date of OPV2 withdrawal. The most intensive mopping up response would be implemented in the highest risk category scenario which would be the detection of cVDPV2 in a Tier 1 country during the October 2015-March 2016 timeframe. Based on the updated tOPV SIA calendar for preventative campaigns and this risk-based strategy, as we approach the OPV2 withdrawal date, a progressively intensified response would be undertaken following detection of any VDPV2.

Figure 1.

Nigeria: persistent cVDPV2 outbreaks, as of 18/3/15, and tOPV (IPV) SIAs conducted and planned from Jan/4 to Mar/16

As of 18 March 2015

Year / Month

Viral grouping	Source	State	2014 Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	2015 Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	2016 Jan.	Feb.	Mar.	Apr.
Nigeria-Old	AFP	Borno			•																									
		Katsina									•																			
		Kano					•	•		•		•																		
		Jigawa										•																		
	ENV	Jigawa											x																	
		Kano				x	x	x	x	x	x	x																		
		Kaduna						x		x		x	x																	
		Sokoto		x		x	x	x	x	x																				
Nigeria-Chad		Borno		•	•	•	•	•			•																		
		Kano							•				•																	
		Jigawa										•																		
		Yobe										•	•																	
	ENV	Borno	x	x	x	x	x	x																						
		Kano				x																								
Nigeria 2014	ENV	Kaduna								x					x															
		SIAs using tOPV or IPV (conducted and *planned*)				SNID: bOPV + tOPV		bOPV SNID plus IPV in HR areas of Borno + Yobe		SNID: tOPV	HR area (which one?) IPV		SNID: tOPV * (IPV in HR areas of Yobe)	SNID: bOPV (+ IPV in 12 Kano LGAs)			NID: tOPV (+ IPV in 8 Kano LGAs)		SNID: tOPV			SNID: tOPV			SNID: tOPV			SNID: tOPV	NID: tOPV	NID: tOPV	end OPV2

• At least one cVDPV2 AFP case reported per given month

x At least one environmental site with a cVDPV2 reported per given month

Figure 2.

Pakistan: persistent cVDPV2 outbreaks (as of 18/3/15) and tOPV (IPV) SIAs conducted and planned,Jan. 2014 to Mar 2016

As of 18 March, 2015

Year / Month

Viral grouping	Source	Province	2014 Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	2015 Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	2016 Jan.	Feb.	Mar.	Apr.
Pakistan: 2 'old' groupings	AFP only	FATA	•	•	•	•	•																							
			•	•				•																						
		KP					•																							
							•																							
Pakistan-New	AFP	Sindh												•																
	ENV	Sindh							x		x	x	x	x	x															
		SIAs using tOPV or IPV (conducted and *planned*)		SNID: bOPV + tOPV	SNID: bOPV + tOPV				NID: tOPV	SNID: tOPV			SNID: bOPV +tOPV plus IPV (76.000) in Quetta		IPV (106.000) in K. Abd., FR Bannu, Karachi	IPV (25.000) in Pishin, BAL	NID: tOPV		NID: tOPV				NID: tOPV		NID: tOPV			SNID: tOPV		NID: tOPV	stop OPV2

• At least one cVDPV2 AFP case reported per given month

x At least one environmental site with a cVDPV2 reported per given month

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Type 2 OPV withdrawal: update on readiness and preparations for the switch

Background

At its October 2014 meeting, SAGE reviewed the status of the five readiness criteria for type 2 oral poliovirus vaccine (OPV2) withdrawal globally, as well as progress towards the elimination of persistent circulating vaccine derived poliovirus type 2 (cVDPV2).

This paper provides an update on progress made towards meeting the OPV2 withdrawal readiness criteria since October 2014 and details work ongoing in preparation for the global synchronised switch from trivalent OPV (tOPV) to bivalent OPV (bOPV).

Update on the five OPV2 withdrawal readiness criteria

1. At least 1 dose of inactivated poliovirus vaccine (IPV) in OPV-using countries

- **IPV introduction**: Introduction of at least one dose of IPV into the routine immunization programs of all countries currently only using OPV is a critical step to ensure OPV type 2 withdrawal can be completed and associated risks mitigated. To date, 15 countries have introduced IPV, and a further 109 have made commitments to do so before the end of 2015. This means that more than 99% of the global birth cohort, including all countries at highest risk for cVDPV2 emergence and circulation, either use IPV or have expressed a commitment or intent to introduce IPV by the end of 2015. In addition, 72 countries have applied to Gavi for IPV introduction support, of which 66 been approved[1]. In December 2014, the Polio Oversight Board endorsed the principle of providing catalytic procurement and financial support to a total of 25 non Gavi countries. Of those, 24 have requested to benefit from this support, i.e., 12 months of IPV procurement support and a one-time "Vaccine Introduction Grant." To date, four country applications have been approved and an additional four applications are under review.

2. bOPV licensed for routine immunization

- **Global bOPV access**: Currently the bOPV license stipulates that the vaccine should be used only in campaigns or for outbreak response activities. In order for the vaccine to be used in routine immunization programs, there must be a

[1] The last six country applications (Armenia, Djibouti, Haiti, Guyana, Honduras and PNG) are being reviewed by the Gavi Independent Review Committee at the time this report is being written. It is expected that they will be approved.

variation of the vaccine label. To date, three manufacturers/fillers have applied to their national regulators for such a label change. Approval is expected by end of Q2/2015. In addition, in order to facilitate rapid access to bOPV, a World Health Assembly resolution will be put forward in May 2015 that will urge member states to grant an exceptional authorization for the use of bOPV in routine programmes based on WHO Pre-Qualification while national licensing procedures are on-going.

3. Type 2 poliovirus surveillance and response protocols and monovalent OPV (mOPV) stockpile

- **Type 2 surveillance:** In October, SAGE endorsed the plans for the expansion of environmental surveillance according to the following criteria:
  - Sustain in endemic areas and expand to capture "silent" areas within endemic countries
  - Establish in priority countries along overland exportation routes
  - Establish in priority areas for cVDPV emergence (ie the Tier 1 countries),

Since the last meeting, new sites have been established in Nigeria, Pakistan and Afghanistan, and site assessments and laboratory capacity building has taken place in a number of countries in Central and West Africa. Further expansion is planned in the Middle East and Horn of Africa.

- **Constitution of a mOPV2 stockpile**: A global mOPV2 stockpile is being established to deal with any OPV type 2 outbreaks that may occur after the withdrawal of type 2 OPV. The protocol for the management and operationalization of the stockpile was endorsed by SAGE in October 2014 which will ensure the rapid detection and confirmation of outbreaks, and deployment of vaccines after authorization by the Director General of WHO. A total of 500 million doses of mOPV2 in bulk have already been secured from two manufacturers. A tender has been issued for filling 100 million of these doses in vials.

4. Appropriate containment and handling of residual type 2 materials

- **Containment**: In October, the strategic approach and plan for fully aligning the containment of polioviruses with the major milestones and timelines of the Polio Eradication and Endgame Strategic Plan 2013–2018 was finalized and endorsed by SAGE. The WHO global action plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of OPV use (called GAPIII) establishes specific measures for the poliovirus type 2 containment phase of the polio endgame; differentiates the requirements for facilities holding wild versus Sabin-strain polioviruses; and sets parameters for

the long-term containment of polioviruses following the eventual cessation of vaccination with all oral poliovirus vaccines after 2019. All Members States are now being approached to update and finalize their inventories of facilities holding wild and Sabin polioviruses which need to be informed of the impending requirements to contain all type 2 polioviruses, including preparations for destruction or containment of all type 2 wild poliovirus (WPV) including vaccine-derived strains by the end of 2015, and type 2 OPV/Sabin within three months of OPV2 withdrawal.

5. Verification of global eradication of wild poliovirus type 2

- **Verification of WPV2 eradication**: Following the WHO Executive Board (February 2015), Regional Directors agreed to write to all member states and invite them to provide a formal statement to the Regional Certification Commissions and to WHO to confirm when WPV2 was last detected in their country . On the basis of the evidence received from regional certification commissions, the Global Certification Commission will then be able to confirm the eradication of wild polio virus type 2. The next Global Certification Commission meeting is planned for the second half of 2015.

Elimination of persistent cVDPV2: The elimination of persistent lineages of cVDPV2 is a pre-requisite to the withdrawal of type 2 OPV. A separate document describes the epidemiological status and the on-going and planned response to persistent cVDPV2.

Update on the planning for the switch from tOPV to bOPV

In addition to ensuring the readiness criteria are met, significant planning is required at all levels to ensure countries have the necessary information, guidance and support to implement OPV type 2 withdrawal and switch from tOPV to bOPV. Key areas of work ongoing are as follows:

- **Technical Guidance and Standard Operating Procedures:** The global switch from tOPV to bOPV is planned to take place during a two week window in April 2016. In order to ensure countries are prepared, detailed guidance notes and standard operating procedures have been developed and distributed. All countries are required to have developed a plan for the switch by the end of Q3/2015. Dry runs will be conducted in a few selected countries during Q2/2015 to simulate the switch itself and identify any unforeseen problems. Technical assistance to countries is available through WHO and UNICEF offices as well as via the STOP team members deployed by the two agencies.

- **Supply:** Managing tOPV and bOPV supplies to ensure there is enough of the right type of vaccine at the right time will be critical to successful implementation of the

switch. Detailed supply planning, under the leadership of UNICEF supply division, is ongoing. Member States are advised and supported to precisely forecast the amount of tOPV they need to avoid over-stocking; this is especially important for self-procuring countries who run not just financial risks with over-ordering of tOPV but the risk of not being able to get sufficient bOPV in time. Special attention is being paid to this area of work and personnel are being recruited to manage it.

- **Communications:** A package of information materials has been developed to provide more detailed information to countries and partners, and support advocacy efforts. These are available on the WHO website[2] and are also being distributed at EPI manager meetings, where sessions on the switch are being conducted. In addition, a series of educational webinars will be held in March for global and regional level partners. At the end of March, a joint letter signed by the Director General of WHO and by the Executive Director of UNICEF will be sent to all 156 tOPV using countries and territories to emphasise the importance of the switch to bOPV as an integral part of the Polio Eradication and End Game Strategic plan.

[2] http://www.who.int/immunization/diseases/poliomyelitis/endgame_objective2/en/

Executive Summary for April 2015 SAGE Session on Administration of Multiple Injectable Vaccines at a Single Visit

Due to the global introductions of pneumococcal conjugate vaccines (PCV) and inactivated polio vaccine (IPV), a majority of countries could soon have national vaccination schedules recommending administration of three or more injectable vaccines to infants during the same immunization visit. The evidence on the safety of administering multiple injectable vaccines, techniques for administering multiple injectable vaccines, and past experiences with healthcare provider and caregiver acceptance of additional injectable vaccinations were reviewed to help provide the basis for guidance in this area.

Summary of field study report: Post-IPV introduction assessment of the acceptability of three vaccine injections given to infants during clinic visits in South Africa, November 2014.

Since 2009, two of the five recommended vaccination visits in the first year of life in South Africa have included 3 injections in one visit, including IPV-containing vaccine at 6,10 and 14 weeks of age. A cross-sectional survey of healthcare providers and infant caregivers at 21 public and 5 private clinics in two provinces was conducted. Most caregivers preferred that all recommended vaccinations be given in one visit rather than deferring one or more; however, the majority also reported that 3 injections or more were too many to give in one visit. Concerns were influenced by perceived infant pain and discomfort. Nevertheless, nearly all caregivers were willing to bring the child for visits with 3 injections again, and 96% of children were up to date for age for their immunizations. About half of the healthcare providers expressed concern about administering 3 injections in one visit. Caregivers' lack of knowledge and understanding of the reasons for 3 injectable vaccines was exacerbated by the limited communication with and information for caregivers from vaccinators. Strategies to improve immunization pain management and communication with caregivers may further improve acceptability of three injections.

Summary of field study report: Pre-IPV introduction assessment of healthcare providers and caregivers' perceptions of multiple injections for immunization in Tanzania, March 2015.

In preparation for IPV introduction in Tanzania (which would increase the number of injections at the 14 week visit to 3), focus group discussions and interviews with healthcare providers and infant caregivers were conducted across 6 regions of Tanzania in early 2015. The majority of healthcare providers believed the additional injection would not affect their work and were comfortable with administering 3 injections in one visit. The providers reported that potential challenges of increased injections included additional infant pain and a possible drop in vaccination coverage; potential benefits of not spreading out vaccinations included maximum protection against disease and increased efficiency for both parent and provider. The majority of caregivers accepted multiple injections as they perceived that young infants cannot rationalize fear of injections, that it is most efficient to get all recommended injections in one visit, and that infants are protected against disease at the youngest possible age. Both parents and providers identified current scenarios where children already receive 3 injections in one visit (such as children catching up on missed vaccinations), so there was already experience with multiple injections.

Summary of systematic review of experiences with provider and parental attitudes and practices regarding the administration of multiple injections during infant vaccination visits, 1970-2014

A systematic review was conducted to examine healthcare provider and infant caregiver concerns and practices related to the introduction of additional injectable vaccinations into routine childhood

vaccination visits. Forty-four articles were identified; 42 were from high income countries, including 21 from the U.S.A. Providers and parents reported concerns regarding multiple injections in one vaccination visit; these concerns increased linearly with the number of injections suggested in one visit. Common parental and provider concerns included apprehension about the pain experienced by the child, worry about potential side effects, and uncertainty about vaccine effectiveness. Multiple studies reported that a positive provider recommendation to the parent and a high level of concern about the severity of the target disease were significantly associated with parental acceptance of all injections. Providers often significantly overestimated parental concerns about multiple injections. Their overestimation of parental concerns may lead them to postpone recommended vaccinations, which may result in extra visits and delayed vaccination. More research is needed on interventions to overcome provider and parental concern about multiple injections, particularly in developing countries.

Summary of systematic review of safety and methods of administering multiple vaccines to infants

A systematic review was conducted in order to provide evidence on the safety and methods of administering multiple vaccines to infants in one visit. The review focused on IPV, DTP-HepB-Hib, and PCV vaccines, but other types of vaccines were included if study results were pertinent. In addition, literature reviews focused on specific subtopics and a grey literature review were conducted if little evidence was available in the initial search of peer-reviewed literature.

No studies were identified that evaluated the non-inferiority of giving two or more injections in the same limb compared to administration in different limbs for infants. In general, simultaneous administration of the relevant vaccines with other routine vaccines was well tolerated among infants; however, there were a few combinations of vaccines that resulted in reported increases in adverse events. Although multiple guidance documents recommend a 2.5 cm separation between injection sites on the same limb to allow for local reactions to be differentiated by vaccine type, no evidence from research was found to support this recommendation. Multiple published reviews have stated that the use of the deltoid muscle for intramuscular injections among infants is not preferable as the muscle is not well enough developed; the vastus lateralis muscle and ventrogluteal site are recommended alternative sites for vaccination. Additionally, studies have repeatedly shown that intramuscular administration of inactivated vaccines provides equal or greater immunogenicity and fewer local reactions than subcutaneous administration. No clear guidelines were identified on a preferred vaccine preparation process for a multiple injection visit.

Relevance of Findings to Country Immunization Schedules

There are 68 countries that have 3 or more vaccine injections scheduled for at least one visit in the country routine childhood immunization schedule. Twenty-six countries are including IPV as the 3rd injection in one visit by April 2016 (as of March 2015).

Key Conclusions and Recommendations (abbreviated)

- IPV (non-adjuvanted) can be safely and effectively given intramuscularly (IM) or subcutaneously (SC). However, the IM route is generally less reactogenic for inactivated vaccines.
- The vastus lateralis (thigh) muscle is a viable site with the ventrogluteal (hip) muscle as an acceptable alternative for intramuscular injections among infants. The deltoid (upper arm) muscle is another viable site for children 12 through 18 months, however the use of the deltoid may need to be delayed if the muscle is atrophied.

- Systematic comparisons of the risks and benefits of the various possible sites for administering infants DTP-Hepatitis B-Hib vaccine, IPV, and a PCV at the same visit are lacking, but injecting DTP-Hepatitis B-Hib vaccine in one thigh and IPV and PCV in another thigh can be done safely and effectively.
- Systematic studies of the best distance for separating vaccine injections are lacking, although a 2.5 cm distance between injections to the vastus lateralis (thigh) or deltoid is a viable option to allow any localized adverse events caused by the individual vaccines be distinguished.
- If multiple injectable vaccines are to be administered in one visit, vaccines needed for an infant should be prepared in a clean designated area, covering each clean needle with its cap using a one-hand scoop technique, and then administering of the indicated vaccines to the infant in quick succession is a viable approach.
- Countries introducing new vaccines should be strongly encouraged to:
    - Ensure healthcare providers receive information that the safety and biologic effects of providing all recommended vaccines in single visits are generally similar to those of providing them in separate visits, as well as training on communication techniques with parents with concerns about the child receiving multiple vaccine injections in a single visit.
    - Develop national vaccination schedules that include multiple vaccine injections in one visit unless specific evidence exists that there are negative repercussions which outweigh the benefits of administering multiple vaccines in one visit.
    - Monitor the acceptance and effects of simultaneous administration of injectable vaccines per their national vaccination schedule recommendations.
- Vaccination schedules should adapt to new data on the adverse events and immunogenicity of specific vaccine combinations as they become available

The acceptability of three vaccine injections given to infants during clinic visits in South Africa

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A Report to the WHO Department of Immunization, Vaccines and Biologicals

November 2014

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1 Abstract

Background: The Expanded Programme on Immunisation (EPI) has grown significantly since its launch by WHO in 1974, with multiple injections currently required to deliver a large number of antigens. Concerns have been expressed that three or

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more injections at a single visit may affect acceptability of immunisations and decrease coverage. This study therefore assessed the acceptability and acceptance of three immunisation injections at a single visit.

Methods: This cross-sectional survey of infants' caregivers and vaccinators at clinics in two provinces of South Africa used quantitative and qualitative methods for data collection and analysis.

Results: In total, 229 caregivers and 98 vaccinators at 21 public and 5 private clinics in rural and urban areas of the Western Cape and KwaZulu-Natal participated in the study. The researchers also observed the administration of 129 three-injection vaccinations. Caregivers were satisfied or very satisfied with the vaccinators' care (n=221; 97%) and immunisation injections (213; 93%), but felt that three injections (118; 51.5%) or more (78; 34.1%) were too many to be given to infants at one clinic visit. However, if three injections were required, most caregivers (166; 73%) preferred one visit for all the injections, while 59(26%) preferred more visits for fewer injections at each visit. The satisfaction with injections did not differ between caregivers attending for the first immunisation visit and those who had been exposed to two immunisation visits for three injections (Chi-square P = 0.192). Acceptance of three injections was high with most caregivers (223; 97%) willing to bring their infant for three injections again, and 220 (96.1%) of the infants were up to date for age for their immunisations. Many (54; 55.1%) of the 80 public and 18 private sector vaccinators expressed concern about giving three injections in one visit. In 122 (95%) observed '3 injection' vaccination sessions, the vaccinators administered all the required vaccinations for that visit. The remaining seven vaccinations were not completed because of stock-outs of particular antigens.

Conclusion: This study found a high acceptance by caregivers and vaccinators of three injections at one immunisation visit, as assessed by their compliance with the EPI programme requirements. However, the acceptability of three injections was a concern, influenced mainly by the perceived pain and discomfort experienced by infants. Caregivers' lack of knowledge and understanding of the reasons for 3 injections was exacerbated by the limited communication with and information for caregivers from vaccinators.

Strategies to improve pain management during immunisations and communication with caregivers may improve acceptability of three injections, and should be evaluated using rigorous research methods as part of the expansion of the EPI in low- and middle-income countries.

Keywords: Expanded Programme on Immunisation, three injections, acceptability, acceptance, immunisation coverage.

2 Background

Vaccines are among the most successful and cost-effective public health interventions available for preventing infectious diseases and deaths in children[1]. Since the World Health Organization (WHO) launched the Expanded Programme on Immunisation (EPI) schedule worldwide in 1974 with six basic antigens (BCG, poliomyelitis (polio), diphtheria, tetanus, pertussis, and measles), there has been a significant expansion in the EPI schedule[2]. Depending on the country, a fully immunised child now needs at least six routine visits to receive between 6 and 13 vaccines in the first year, and from 13 to 20 injections by 2 years of age. Protection is provided against 16 infectious vaccine preventable diseases including measles, mumps, rubella, varicella, hepatitis B, diphtheria, tetanus, pertussis, *Haemophilus influenza*e type b (Hib), polio, influenza (flu), rotavirus, and pneumococcal disease.[2,3] Despite the availability of combination vaccines, multiple injections are required at several EPI visits in order to deliver all the recommended antigens. Caregivers (persons who bring children for immunisation) may have concerns about multiple injections at a single immunisation visit[4, 5].

Many low- and middle-income countries (LMICs) are introducing new and under-utilised injectable vaccines, especially in the context of global health initiatives [2]. More infants in LMICs will therefore receive multiple injections during the same clinic visit, leading to concerns about the acceptability and effect of this practice on EPI programmes in those countries. While some studies describe the acceptability of multiple vaccine injections in high-income countries, [5, 6, 7] there is little systematic information from LMICs to inform decision making.

South Africa (SA) has included three vaccination injections during a single immunisation visit since the introduction of pneumococcal vaccine in April 2009, and two of the five EPI [SA] visits in the first year of life require three injections[8]. The EPI [SA] therefore provides an appropriate setting to assess acceptability and acceptance of three injections at a single visit to inform practices in other LMICs.
The aim of this study was to determine the acceptability and acceptance of three injections during a single EPI visit, and factors influencing this among caregivers and vaccinators in South Africa.

3 Methods

The study population for this cross-sectional survey consisted of caregivers of infants between 6 weeks and 6 months old, and vaccinators at public and private primary healthcare facilities offering EPI services in rural and urban areas in the Western Cape and KwaZulu Natal provinces of South Africa. Facilities were purposively selected based on the EPI service volumes, geographical location and populations served, in consultation with Municipal and Provincial Departments of Health, and private health service providers. All caregivers 18 years and older with infants aged between 6 weeks and 6 months, attending the health services on the days of the survey, and all health service staff at those services who had conducted vaccinations within the past year were invited to participate. A sample size of 200 caregivers was estimated based on the 2012/2013 national immunisation coverage rate of 80.1%, with a +/-5% precision[9]. The study aimed to include 50 vaccinators from each Province in the survey. A pilot study was conducted to finalise the data collection tools and procedures. The questionnaires, including closed and open-ended questions for caregivers and vaccinators, were translated into the key languages of the two provinces (English, Afrikaans, *isi*Xhosa, and *isi*Zulu) and administered by trained research assistants in the language of the participant. An observation checklist was used to record actual practices of vaccinators during the administration of multiple-injection vaccinations. Caregivers were interviewed after the infant had received the vaccination or other services at the clinic.

Acceptability and acceptance of three immunization injections at one visit were the main outcomes assessed. Acceptability was measured as the caregivers' and vaccinators' knowledge, perceptions of the benefits of, and expressed preferences regarding three injections during a single EPI visit. Acceptance was measured by two variables. Firstly, as the expressed intention or willingness to accept (caregivers) or provide (vaccinators) three injections during a single EPI visit, and secondly by the actual acceptance of or provision of three injections as measured by completion of the prescribed immunisation schedule and vaccinators' compliance with EPI policy.

The questionnaires were loaded onto a software package which allowed for data collection using mobile phones. Data were uploaded from mobile phones directly into an electronic research console (Microsoft Access database) on a daily basis for quality checks and data storage. The cleaned data were exported to STATA version 13 for analysis. Statistical tests such as chi-square and t-tests were used to assess the significance of associations and differences. Open-ended questions were analysed through coding and category development, and quantified (number count). Ethical approval (Ref #: N14/06/062) was provided by the Research Ethics Committee of the Faculty of Medicine and Health Sciences, Stellenbosch University, and all requirements for the ethical conduct of research were adhered to.

4 Results

Two hundred and twenty nine caregivers at nine public and four private EPI clinics (Table 1) in rural and urban areas of the Western Cape (WC) and KwaZulu-Natal (KZN) participated in the survey. The caregivers were mainly the infants' mothers (210; 91.7%), female (226; 98.7%), young (median age 26.9, range 18.0 to 69.8), single (149; 65.0%), and had high school or higher levels of education (221; 96.5%). More caregivers were from the WC (132; 57.6%) than from KZN (97; 42.4%). There was no significant difference in age and education of caregivers from the two provinces (Table 5). However, there were more single (82; 84.5%) caregivers in KZN than in the WC (67; 50.7%) (Chi-square $P < 0.001$), and more children in KZN (14.4%) than in WC (2.3%) were brought to the clinic by someone other than their mother or father ($P = 0.001$). Private sector caregivers were older, better educated, and more likely to be married than public sector caregivers (Table 6). However numbers in the private sector were small and all were from the WC.

The median age of the infants was 14.3 weeks (range 5.3 to 29.6), and 117 (51.1%) were female (Table 2). The gender ratio of infants attending the facility differed between the two provinces, with more female infants in KZN (60.8%) than in the WC (43.9%) ($P = 0.012$). Most were attending the clinic for an immunisation visit (163; 71.2%), of whom 93 (40.6%) were attending for the first (6 week) three-injection immunisation visit. Other reasons for attendance included growth monitoring (25; 10.9%) and an illness episode (21; 9.1%). More infants in the WC (83.3%) were attending specifically for immunisation than in KZN (54.6%) ($P < 0.001$). Of the 229 infants, 124 (54.2%) had previously completed or were completing the 14 week immunisation injection at that visit. At the 'study' visit 138 (60.3%) infants received three injections.

4.1 Acceptability of three injections to caregivers

Caregivers' understanding of the purpose of immunisation was that it protected the infant from disease or kept the infant healthy (202; 88.2%), and prevented the spread of disease or epidemics (23; 10.4%) (Table 3). Few caregivers knew the specific diseases which the EPI vaccines protected their infants against, with tuberculosis (89; 38.9%), polio (77; 33.6%) and measles (28; 12.2%) most commonly cited. Caregivers' main sources of information about immunisations had been nurses or doctors (164; 71.6%) and family (15; 6.6%). Many (162; 70.7%) caregivers had been informed about the number of

immunisation injections received by the infants, with more WC caregivers (79.8%) informed than KZN caregivers (60.8%) (P = 0.005) (Tables 3 & 5).

Approximately half of the caregivers felt that three injections (118; 51.5%) were too many to be given to infants at one clinic visit. More KZN caregivers felt that three or more injections were too many than WC caregivers (P = 0.004) (Table 5). The main concerns were the infants' immediate pain and distress, and subsequent discomfort. The pain experienced by the infant (n=119) and the caregiver's perception of the infant as too young and small (n=39) when receiving the three injections were major concerns.

"It's too much and too painful"
"It's too painful and leads to sleepless nights for the infant"
"They are still too tiny and fragile"

"The babies are still too young for 3 injections"
"The infant is too young and it felt like they are in deep pain when they were injected"

However, if three injections were required, most caregivers preferred one visit for the three injections (166; 72.5%), while 59 (25.8%) preferred more visits for fewer injections at each visit (Table 3). More KZN caregivers (33%) indicated a preference for additional visits than WC caregivers (20.5%) (P=0.004) (Table 5). There was no significant difference between the private and public sectors, and age of their infant, in caregivers' preference for additional clinic visits to reduce the number of injections received at each (Table's 6 & 7).

Caregivers expressed satisfaction with immunization services received, with 221 (96.5%) satisfied or very satisfied with the vaccinators' care, and 213 (93.0%) satisfied or very satisfied with the immunization injections (Table 3, Annex A). WC caregivers were more satisfied with the injections (97%) than KZN caregivers (87.6%) (P = 0.006). Satisfaction with injections or vaccinators care did not differ across the sectors, nor did satisfaction with injections differ between caregivers of infants attending for the first three-injection immunization visit (i.e. 6 weeks), and those with older infants who had been exposed to two immunization visits for three injections (P = 0.192) (Table 5). However, caregivers of six week old infants were more dissatisfied with the vaccinators care than caregivers of older infants (P =0.006) (Table 7). Vaccinators also reported that caregivers of six week old infants expressed unhappiness about the three injections 'always or often' (57.1%) compared to caregivers of babies older than six weeks who expressed such unhappiness less frequently (19.4%) (Table 12).
Caregivers satisfaction with immunisation injections was informed by their beliefs that it protected against disease (n=113) and improved the infant's health (n=38).)

"Because I know that it is good for the child's health and well-being"
"If the child gets all the injections while little they won't get ill when they are bigger"

The infant's response to the injection (n=28) also contributed to the level of satisfaction with the immunisation services, with dissatisfied caregivers indicating that the infant's emotional response and possible side-effects were important factors.

"Pain; The baby cries and does not sleep at night"
"By taking different injections at different times it makes me unhappy because that makes babies cry a lot"
"I am not sure whether my grandchild won't have complications. I am also wondering whether the baby will sleep tonight"

The caregivers' satisfaction with the vaccinators was influenced by the vaccinators' handling of the infant (n=83) and attitude towards the caregiver (n=75).

"I am happy with the sister's positive attitude but besides generally the staff at this clinic is friendly. I am supposed to use [x] Clinic but I decided to use this clinic because of positive staff attitudes".
"It's the way they handle her. They were caring"

Caregivers also indicated that communication by vaccinators (n=35) and the competency of the vaccinators (n=20) contributed to the level of satisfaction with the vaccinators.

"She is patient; she does not shout at us and she answers our concerns and questions so well"
"Nurse administered injections very well"
"Very quick and efficient"

4.2 Acceptance of three injections by caregivers

Despite feeling that three injections were too many at one immunization visit, most caregivers (223; 97.4%) were willing to bring their infant for 3 injections again, or to recommend that others bring their infants for 3 injections (227; 99.1%) (Table 4). There was no significant difference between the provinces, sectors, and caregivers of 6 week old and those of older infants in willingness to bring the infant for three injections per visit in the future (P =1.000) (Table 7).

Reasons given for caregivers willingness to bring infants for 3 injections in the future were mainly to improve the infant's health (n=113), and to protect against diseases (n=86).

"I only do it for the child's sake because I know that he will be safe from getting sick"
"To protect my child from diseases that attack little babies"

Although caregivers felt they had no choice in the number of injections given per visit, they perceived the injections as an important part of the infant's health routine. Reasons for not returning for 3 injections were related to the infant or the caregiver's discomfort with multiple injections. .

"Three injections given in one day is too much for the infant"
"I cannot watch my granddaughter going through torture"
"Seeing the baby cry makes me to be emotional. I also feel like crying"

A few caregivers (n=5) indicated that convenience positively influenced their willingness to bring the infants for 3 injections in the future.

"It's easier to come for it at one time than driving up and down as this could become difficult"

The benefit of immunisations for the infants' health (n=121) and protection against disease (n=95) were also the main reasons for recommending three injections at one visit to others. Although caregivers were willing to bring their child for three injections again, or to recommend three injections to others, they also expressed the need for changes such as decreasing the number of injections during a single visit by combining injections (n=72) or substituting injections with oral drops (n=46).

"Must be converted to one injection"
"They must give less than 3 injections per visit"
"Please change injections to oral drops if possible"
"Can the injections be changed to oral drops?"

An important measure of acceptance is the extent to which the infants have completed all immunisations required for their age. We found that two hundred and twenty (96.1%) of the infants were up to date for age for their immunisations based on the patient-held immunisation record. A few of the 4 to 6 month old infants (7) were not up to date for age with immunisations. As none of the first visit babies had missed immunisations, it was not possible to do a statistical comparison (Table 4).

4.3 Vaccinators

Of the 98 vaccinators at 21 public and 5 private EPI clinics who participated in the study, most were professional nurses (75; 76.5%), and female (89; 90.8%), with a median age of 43.2 years (range 24.7 to 69.3) (Table 9). More vaccinators were from the WC (68.4%), public sector (81.6%) and urban areas (79.6%). They were experienced with 47 (48.0%) administering EPI vaccines for more than five years, and a further 36 (36.7%) between one and five years. More vaccinators in the WC were professional nurses than in KZN (P =0.013), and had more years of EPI experience (P = 0.028) (Table 14). Almost all the vaccinators in the private sector were professional nurses (P = 0.030), and had more years of EPI experience than the public sector nurses (P = 0.019) (Table 15). Most vaccinators had received EPI training (76; 77.6%), with 37 (37.7%) having had training in the last five years, and a further 18 (18.4%) in the last year. They had learnt to administer multiple injections mainly through formal training programmes (37; 37.8%); training by a colleague (15; 15.3%), on the job supervision or mentoring (16; 16.3%), and training sessions with vaccinators from other health facilities (15; 15.3%) (Table 9).

Most vaccinators (97; 99.0%) felt it was very important to provide information about three injections to caregivers. Fewer (54; 55.1%) said they always provided explanations about the reasons for multiple injections, and only 27 (27.6%) indicated that they were the main source of information about multiple immunisation injections for caregivers (Table 10). More KZN vaccinators (83.9%) indicated that they always explain the reasons for multiple injections compared to the WC (41.8%) (P =0.002) (Table14). Private sector vaccinators also explained the reasons for multiple injections more frequently that the public sector vaccinators (P= 0.013).

Researchers observed the administration of 129 vaccinations involving three injections (Table 11). The vaccinators explained the importance of the infant being fully immunized in 69 (53.5%); explained the procedures in 84 (65.1%); provided counselling on side effects in 26 (20.2%); and informed the caregivers to return for the next immunization visit in 66 (51.2%) of the 129 multiple injection vaccinations observed (Table11). KZN vaccinators counselled the caregivers more frequently about side effects than WC vaccinators (P = 0.051), and about returning for the next appointment (P = 0.019) (Table 14). Private sector vaccinators were observed to provide information on side effects (81.25%; P < 0.001), and future immunization dates (75%; P = 0.042) more frequently than public sector vaccinators (11.5% and 47.79% respectively) (Table 15).

Acceptability of three injections to vaccinators

Most vaccinators (54; 55.1%) expressed some concern about giving three injections in one visit, with 24 (24.5%) being very concerned. Public and private sector vaccinators did not differ in their level of concern, but KZN vaccinators expressed higher levels of concern than WC vaccinators (P < 0.001). The vaccinators main concerns were the crying and pain experienced by the infants (32; 59.3%), possible side effects (6; 11.1%) and caregivers objecting or not returning for subsequent immunization visits (10; 18.5%). In addition, 49 (50.0%) of vaccinators felt that 3 injections were too many at one visit (Table 12). The vaccinators years of EPI experience was not associated with their views on the number of injections which were acceptable during a single visit (P = 0,843) (Table 16).

Vaccinators stressed the importance of preparing caregivers prior to administering the injections (n=30) and caregiver education (n=23) to facilitate administering multiple injections.

"If the parents understand the reason why their kids are getting the injections. Explain the importance and giving them evidence based facts on the importance of immunisations."

"Speak and explain the procedure to the mother so that she's comfortable."

The main challenges they faced when giving multiple injections included caregiver's (n=21) and infant's (n=15) emotional responses and their own concerns about high risk infants (n=10).

"When the mums are tense, it makes it difficult. Also just seeing the baby cry breaks my heart"

"Babies are crying a lot which makes it hard to work"

"...also if the mother doesn't want the injection. Also when babies are premature and abnormal babies e.g. physical disabilities."

Vaccinators' suggestions to improve the acceptability of 3 injections included giving more caregiver education (n=58) and fewer injections (n=40). Several vaccinators also recommended combining injections and changing the mode of vaccine delivery to oral drops.

"Educating moms on a regular basis makes the process better"

"Proper education for mothers so that they know the reasons for immunisation"

"Combining injections because mums complain about the pain the baby gets subjected to"

"It would help to give oral drops instead of injections because mums always exclaim when I mention that the baby will get 3 injections."

4.4 Acceptance of three injections to vaccinators

In terms of compliance with EPI policy, 93 out of 98 (94.9%) vaccinators were able to produce the standard written protocols for immunisations (Table 10), and 136 (98.6%) injections were given in the infants' thighs as prescribed by the national EPI [SA] policy[8] (Table 2).

However, a number of infants (19; 14.7%) were vaccinated while lying unsupported on the examination couch (Table 11), contrary to the national EPI [SA] policy which recommends that the infant be securely held on an adult's lap.[8] A few vaccinators (10; 10.2%) also regularly advised caregivers to bring their infants for extra visits to have fewer immunisations at each visit (Table 13). This occurred more frequently in KZN than in WC (P < 0.001) (Table 14), but did not differ between the private and public sectors (P = 0.987) (Table 15).

In 122 (94.6%) of the 129 observed vaccinations (Table 11), the vaccinators administered all the vaccines that were due on that visit. The seven injections that were not administered were due to stock-outs of particular antigens, and caregivers were advised to return for those.

5 Discussion

The high proportion of single mothers in this survey is similar to that in the general population with only 31.3% of mothers of children 0- 4 years legally married, and no information on paternity in 66.6% of all birth registrations in South Africa. [10, 11] The reason for the higher proportion of single mothers in the KZN sample is not clear. Study caregivers had higher levels of secondary education than mothers of children aged 0-4 in the general population, with 85.7% versus 76.1% having some secondary level education or having completed high school[10]. This is consistent with previous studies from South Africa and sub-Saharan Africa where caregivers with secondary or higher education levels were more likely to have their children immunized compared to those with lower education levels.[12, 13] The urban rural mix of participants and facilities surveyed is similar to the distribution of the population in the Western Cape, but less rural than South Africa.[10] The older age, higher education levels, and marital status of the private sector caregivers is consistent with the higher economic group that these caregivers represent. The sample of infants included a large proportion who were attending for the first multiple injection vaccination at 6 weeks, and enabled a comparison of their experiences with those of caregivers of older infants who had

prior experience of multiple injection vaccinations. Caregivers using private facilities (5.4%) are underrepresented compared to the approximately 16% of the South African population who have private health insurance.[15]

The age and gender distribution of vaccinators in this study is similar to national data on nurses in South Africa, with the highest concentration of nurses in the age group 40-49 years, and few males. [14] More vaccinators in the study were professional nurses (76.5%) compared to their representation (51.4%) amongst all nurses in South Africa.[14] Professional nurses have a four year academic qualification and are qualified to administer vaccinations, but also have to supervise immunisations done by enrolled nurses (2 year basic nurse training programme).

Vaccinators differed between the provinces with fewer professional nurses and less EPI experience in KZN. This may have contributed to the higher levels of concern by KZN vaccinators about multiple injections, and their tendency to advise caregivers to return for extra visits to receive fewer injections at each visit. KZN vaccinators claim to frequently explain the number of injections, was confirmed in the few observations in KZN where they provided more counselling and information than WC vaccinators. However the caregiver responses indicated that WC caregivers were more informed about the number of injections, and less dissatisfied with the injections than KZN caregivers. KZN caregivers also expressed a stronger preference for more visits, which may reflect the KZN vaccinators' tendency to advise them to return for more visits. Private sector caregivers received more information and counselling than public sector caregivers. The lack of any statistical differences in acceptability and acceptance of multiple injections may be due to the very small numbers of private caregivers in the study.

A worrying finding is that approximately half of caregivers and vaccinators felt that 3 injections were too many at one visit. Their concerns were based on the infant's pain and distress during the injection procedure and their discomfort afterwards, and was greatest for the younger infants

Acceptability is influenced by the clients' perceptions of the benefits versus the risks or costs of the care provided. [16] Improved knowledge and understanding of the benefits of the injections infants receive could assist in mitigating the concerns of caregivers about the infants distress at the time of the immunisation. Most caregivers had a basic knowledge of the purpose of immunisations, but lacked further knowledge of the diseases that their infants were being protected against, and many were not informed about or prepared for the three immunization injections. Their knowledge about tuberculosis and polio immunisations is perhaps a reflection of health education during the antenatal or perinatal period regarding the administration of the BCG and first polio oral drops at birth. Although vaccinators at EPI services recognized the importance of caregivers receiving appropriate information, public sector vaccinators particularly did not routinely provide relevant information. Caregivers indicated that more information would be helpful to assist them in understanding the immunization programme for their infants.

Studies advocate strategies to improve communication between health care providers and caregivers regarding vaccinations, [17] but there is a scarcity of evidence on such strategies to improve knowledge and understanding of vaccinations in LMICs. A systematic review of face to face education on knowledge or understanding of vaccinations reported inconsistent improvements in either immunization rates or caregiver understanding of vaccination. [18] However, a review of interventions for improving coverage of childhood immunisations in LMICs found moderate-certainty evidence that health education (community based, facility based and facility plus reminders) improves immunization coverage.[19]

Despite the extensive concerns of caregivers about the infants' pain and discomfort, and their preference for fewer injections, they were largely satisfied with the injections and vaccinators care. However, to reduce the perceived risks or discomforts of multiple injections, better pain management for the infant during the procedure could also contribute to improving acceptability of multiple injections. Evidence based guidelines for reducing injection pain recommend measures such as breastfeeding or administration of a sucrose solution to the infants during the immunization procedure, not placing the infant supine but holding the infant securely during the injections, and other injection and psychological techniques.[20, 21] EPI guidelines and vaccinator training should be updated with such evidence based practices to reduce the distress experienced by infants, their caregivers and the vaccinators during the administration of multiple injections. These measures are particularly important for younger infants coming for the first 3 injection visit, and whom caregivers and vaccinators were most concerned about.
Caregivers and vaccinators also recommended more combined injections or alternative delivery systems such as oral drops to reduce the number of injections given, particularly for 6 week old infants. Despite their concerns, most caregivers expressed a preference for the administration of all 3 injections at one visit if they were deemed necessary. If the practice of advising caregivers to come for additional visits to reduce the number of injections at each visit as found in KZN is more widespread in South Africa, it may undermine this preference of parents with serious implications for the EPI programme.

Acceptance has been defined as 'compliance with vaccinations by a public which yields to the recommendations and social pressure of health workers and community leaders'.[22] The compliance of caregivers with the requirements of the EPI

translated into a high acceptance of 3 injections at one visit, as demonstrated by the expressed willingness of caregivers to return for 3 injections in the future, and the high proportion of infants who were up to date for age for their immunisations. However, as the study represented caregivers who were attending health facilities, it would not have detected infants who failed to return for subsequent immunisations.

Although the acceptability of 3 injections was a concern for vaccinators, this generally did not affect their practices, with vaccinators demonstrating a high compliance with the policies and the administration of vaccines according to the EPI [SA] schedule.[8] Acceptance of three injections at one visit was high, and did not differ between the sectors, or the Provinces, despite several significant differences in the profile of caregivers and vaccinators, their practices and the acceptability of 3 injections at one visit.

5.1 Implication of the findings

A lack of knowledge and understanding of the reasons for immunisations could be an important contributor to the high burden of unimmunized children in parts of sub-Saharan Africa. [13] This has implications for the increase in the number of injections which infants in LMICs may require in the expanded EPI. Although acceptance of 3 injections was high for caregivers attending health services in South Africa, the lower acceptability of 3 injections particularly for the first multiple injection immunisations is a concern. Innovative strategies of educating caregivers on vaccinations are needed, particularly for caregivers with less education or who are not attending health services. The high level of concern about the pain and distress experienced by infants should also be addressed in the training of vaccinators by including evidence-based practices for reducing pain in the administration of vaccine injections [20, 21]

Further research to assess the effects of the expansion of multiple injections in LMIC's on the acceptability and acceptance of EPI in different settings is needed, with a more rigorous study design and larger sample sizes to assess factors contributing to acceptability and acceptance. In addition research on strategies to improve acceptability and acceptance of multiple injections in LMIC's should be undertaken. Further vaccine development is also needed to reduce the numbers of injections administered at each visit in the EPI programme.

5.2 Limitations

The sampling of facilities was stratified to ensure geographic and socio-economic representation from the two Provinces. However, recruiting facilities and participants proved to be more difficult from Kwazulu Natal and the private sector. The study therefore includes more public sector and Western Cape participants. The stratified analysis between the Provinces and sectors was limited because of small numbers in subgroups, and needs to be interpreted with caution. The study only included caregivers who attended health facilities for EPI or other services and may therefore not be representative of the population of caregivers in South Africa. The level of acceptability and acceptance of 3 injections may differ in caregivers with lower levels of education and who do not attend health facilities. Multiple regression analysis was not feasible because of the small sample size and data distribution.

6 Conclusions

This study found no evidence of reduced acceptance by caregivers and vaccinators of 3 injections at a single immunisation visit amongst health service attenders in South Africa. However, the acceptability of 3 injections was a concern for caregivers and vaccinators. Acceptability for caregivers was influenced mainly by the infant's pain and distress. but exacerbated by limited communication and information about EPI and 3 injections at one visit for caregivers. Strategies to improve communication with caregivers may improve the acceptability of 3 injections at one visit. Training of vaccinators should include improving communication and techniques for reducing injection pain in routine vaccinations. Further studies in different settings to understand factors contributing to acceptability and acceptance, as well as evaluations of strategies to improve acceptability and acceptance of multiple immunization injections should be conducted using rigorous research methods as part of the expansion of the EPI in LMIC's.

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9 Annex A: Summary Tables

9.1 Caregivers

Table 1: Description of caregivers (N = 229)

Variable	Categories	n (%)
Province	KwaZulu Natal	97 (42.36)
	Western Cape	132 (57.64)
Location	Urban	173 (75.55)
	Rural	56 (24.45)
Sector	Private (4 clinics)	12 (5.4)
	Public (9 clinics)	217 (94.76)
Age categories (years)	<25	92 (40.17)
	25-34	96 (41.92)
	35-44	30 (13.10)
	45+	11 (4.80)
***Age**	Mean: Median: Range:	28.56 26.87 18.03- 69.84
Gender	Male	3 (1.31)
	Female	226 (98.69)
Education level	Tertiary level	26 (11.35)
	Matric	97 (42.36)
	High School	98 (42.79)
	Primary School	7 (3.06)
	None	1 (0.44)
Marital status	Married	63 (27.51)
	Single	149 (65.07)
	Life Partner	13 (5.68)
	Widowed	2 (0.87)
	Divorced	2 (0.87)
Relationship to child	Mother	210 (91.70)
	Father	2 (0.87)
	Aunt	5 (2.18)
	Sister	1 (0.44)
	Grandmother	9 (3.93)
	Other	2 (0.87)
Brought a child for immunisation in the past year	Yes	127 (55.46)
	No	102 (44.54)
Which immunisation?	6 weeks	28 (22.05)
	10 weeks	26 (20.47)
	14 weeks	53 (41.73)
	Other	20 (15.75)

* Description of age as a continuous variable

Table 2: Description of infants (N = 229)

Variable	Categories	n (%)
***Age**	Mean	14.38
	Median	14.29
	Range	5.28- 29.57

Age categories	6 weeks	93 (40.79)
	4 and 6 months	135 (59.21)
	Other (age missing)	1 (0)
Gender	Male	112 (48.91)
	Female	117 (51.09)
Reasons for visiting the Clinic today	Immunization visit	163 (71.18)
	Baby is sick	21 (9.17)
	Growth monitoring	25 (10.92)
	Follow up visit for a health problem	3 (1.31)
	Other	17 (7.42)
Which immunizations has baby had including today	6 Weeks	227 (99.13)
	10 Weeks	131 (57.21)
	14 Weeks	124 (54.15)
	Other (Vitamin A drops)	10 (4.37)
Number of injections received at visit	1 injection	4 (1.75)
	2 injections	14 (6.11)
	3 injections	138 (60.26)
	Don't know	1 (0.44)
	Not applicable	72 (31.44)
Where were injections given	Combination RRL (2 x right thigh & 1 left thigh)	120 (52.40)
	Combination LLR (2 x left thigh & 1 right thigh)	16 (6.99)
	Upper arms	1 (0.44)
	Other	1 (0.44)
	Can't remember	1 (0.44)
	Not applicable	64 (27.95)
	<=2 injections	26 (11.35)

* Description of age as a continuous variable

Table 3: Acceptability of multiple injections to caregivers (N = 229)

Variable	Categories	n (%)
Caregivers understanding of the purpose of immunization	To protect them from disease	133 (58.08)
	To keep babies healthy	69 (30.13)
	Keep up to date	3 (1.31)
	To prevent other children getting ill	7 (3.06)
	To prevent epidemics	16 (6.99)
	Don't know	1 (0.44)
Caregiver informed about the number of immunization injections infant would receive	Yes	162 (70.74)
	No	67 (29.26)
Source of information about immunisations	Family	15 (6.55)
	Neighbours/friends	8 (3.49)
	Nurses/doctors	164 (71.62)
	Poster or pamphlet from hospital	9 (3.93)
	Health promoter	12 (5.24)
	School teacher	2 (0.87)
	Newspapers/magazines or TV	4 (1.75)
	Other	15 (6.55)
Caregivers knowledge of diseases immunisations protect against	Pneumonia (Pnuemococcal or Hib)	3 (1.31)
	Diarrhoea (rotavirus)	8 (3.49)
	Measles	28 (12.23)
	Polio	77 (33.62)
	Hepatitis B	4 (1.75)
	Diptheria	6 (2.62)

	Tetanus	3 (1.31)
	Whooping cough (Pertussis)	11 (4.80)
	TB	89 (38.86)
Satisfaction with injections received (1)	Very satisfied	87 (37.99)
	Satisfied	126 (55.02)
	Neither satisfied nor dissatisfied	13 (5.68)
	Dissatisfied	3 (1.31)
†Satisfaction with injections (2)	Satisfied	213 (93.01)
	Dissatisfied	16 (6.99)
Satisfaction with provider's care (1)	Very satisfied	85 (37.12)
	Satisfied	136 (59.39)
	Neither satisfied nor dissatisfied	3 (1.31)
	Dissatisfied	5 (2.18)
†Satisfaction with provider's care (2)	Satisfied	221 (96.51)
	Dissatisfied	8 (3.49)
Too many injections at one visit	1 injection	3 (1.31)
	2 injections	17 (7.42)
	3 injections	118 (51.53)
	More than 3 injections	78 (34.06)
	Uncertain	13 (5.68)
Prefer one or more visits for multiple injections	One visit for 3 injections	166 (72.49)
	More visits for fewer injections each	59 (25.76)
	Other	4 (1.75)
Ever told to come for more visits for multiple injections	Yes	35 (15.28)
	No	193 (84.28)
	Uncertain	1 (0.44)

† Same variable as (1), re-categorised into two

Table 4: Acceptance of multiple injections by caregivers (N= 229)

Variable	Categories	n (%)
Willingness to bring child for 3 injections again	Yes	223 (97.38)
	No	2 (0.87)
	Uncertain	4 (1.75)
Willingness to recommend 3 injections to others	Yes	227 (99.13)
	No	1 (0.44)
	Not sure	1 (0.44)
Proportion of infants who are up to date for age on immunisations (ie acceptors)	Yes	220 (96.07)
	No	7 (3.06)
	RTH card not available	2 (0.87)

Table 5: Comparison of caregivers, acceptability and acceptance of multiple injections between Provinces

Variable	Category	Province		Chi-square P-value
		KwaZulu Natal	Western Cape	
Age	<25	41	51	0.580
	>=25	56	81	
Education	Tertiary	9	17	0.098
	Matric	51	46	
	High School	35	63	
	Primary	2	5	
	None	0	1	

Marital status	Married	10	53	<0.001
	Single	82	67	
	Other	5	12	
Sector	Private	0	12	0.001
	Public	97	120	
Relationship to child	Parent	83	129	0.001
	Other	14	3	
Infants gender	Male	38	74	0.012
	Female	59	58	
Reason for visit	Immunisation	53	110	<0.001
	Other	44	22	
Informed about number of injections	Yes	59	103	0.005
	No	38	29	
Satisfaction with injection	Satisfied	85	128	0.006
	Dissatisfied	12	4	
Satisfaction with provider's care	Satisfied	92	129	0.241
	Dissatisfied	5	3	
Too many injections at one visit	One	2	1	0.004
	Two	13	4	
	Three	47	71	
	More	34	44	
	Uncertain	1	12	
Number of visits preferred	One	61	105	0.004
	More	32	27	
	Other	4	0	
Will come for multiple injections again	Yes	93	130	0.400
	No	1	1	
	Uncertain	3	1	
Will recommend multiple injections	Yes	96	131	0.351
	No	1	0	
	Unsure	0	1	
Immunisations up to date for age	Yes	93	127	P=0.195 Fisher's Exact
	No	2	5	
	No card	2	0	

Table 6: Profile of caregivers, acceptability and acceptance of multiple injections by sector

Variable	Category	Sector		Chi-square P-value
		Private	**Public**	
Age (or mean age)	<25	1	91	0.021
	>=25	11	126	
Education	Tertiary	7	19	<0001
	Matric	5	92	
	High School	0	98	
	Primary	0	7	
	None	0	1	
Infants age	6 weeks	3	90	0.253
	4 and 6 months	9	126	
Marital status	Married	9	54	0.006
	Single	3	146	
	Other	0	17	
Satisfaction with injections	Satisfied	12	201	0.329
	Dissatisfied	0	16	

Satisfaction with vaccinator's care	Satisfied	12	209	0.498
	Dissatisfied	0	8	
Number of injections too many at one visit	1 injection	0	3	0.654
	2 injections	0	17	
	3 injections	5	113	
	> 3 injections	6	72	
	Uncertain	1	12	
Preferred frequency of visits	One visit	11	155	0.349Fisher's exact
	More visits for fewer injections	1	58	
	Other	0	4	
Willingness to bring child for 3 injections again	Yes	12	211	Chi2= 0.843 Fisher's exact = 1.000
	No	0	2	
	Uncertain	0	4	
Willingness to recommend 3 injections to others	Yes	12	215	0.946 Fisher's exact= 1.000
	No	0	1	
	Uncertain	0	1	
Immunisations up to date for age (ie acceptors)	Yes	12	208	0.772
	No	0	7	
	No card	0	2	

Table 7: Caregiver profile, acceptability and acceptance of multiple immunisations by infants age (proxy for prior exposure to multiple injections)

Variable	Category	6 Weeks	4 and 6 months	Chi-2 P value
Province	Kwazulu Natal	37	60	0.484
	W Cape	56	75	
Location	Urban	77	96	0.043
	Rural	16	39	
Sector	Public	90	126	0.253
	Private	3	9	
Caregiver age (or means)	< 25	37	55	0.885
	>= 25	56	80	
Education	Tertiary	12	14	0.649
	Matriculated	43	54	
	High school	36	61	
	Primary school	2	5	
	None	0	1	
Marital status	Single	60	89	0.861
	Married	25	37	
	Other	8	9	
Relationship to child	Parent	85	126	0.585
	Other	8	9	
Infants gender	Male	53	59	0.049
	Female	40	76	
Reason for visit	Immunisation	90	72	
	Other	3	63	
Informed about number of injections	Yes	64	98	0.537
	No	29	37	
Satisfaction with injection	Satisfied	84	128	0.192
	Dissatisfied	9	7	
Satisfaction with provider's care	Satisfied	86	134	0.006
	Dissatisfied	7	1	

Too many injections at one visit	One	2	1	0.705
	Two	5	12	
	Three	51	67	
	more	30	47	
	Uncertain	5	8	
Number of visits preferred	One	70	95	0.639
	More	22	37	
	Other	1	3	
Will come for multiple injections again	Yes	90	132	1.00
	No	1	1	
	Uncertain	2	2	
Will recommend multiple injections	Yes	92	134	0.343
	No	1	0	
	Not sure	0	1	
Immunisations up to date for age	Yes	93	126	0.04 Fisher exact P=0.023
	No	0	7	
	Card not available	0	2	

Table 8: Satisfaction with injection by caregiver age category

Variable	Categories	< 25	>=25	Chi-2 P value
Satisfaction with injection	Satisfied	86	127	0.821
	Dissatisfied	6	10	
Too many injections at one visit	One	1	2	0.196
	Two	11	6	
	Three	46	72	
	More	31	47	
	Uncertain	3	10	
Will recommend multiple injections	Yes	91	136	0.339
	No	0	1	
	Not sure	1	0	
Will come for multiple injections again	Yes	90	133	0.792
	No	1	1	
	Not sure	1	3	
Too many injections at one visit	One	1	2	0.201
	Two	11	6	
	Three	46	72	
	More	31	47	
	Uncertain	3	10	

9.2 Vaccinators

Table 9: **Description of vaccinators** (N = 98)

Variable	Categories	n (%)
Province	KwaZulu Natal	31 (31.63%)
	Western Cape	67 (68.37%)
Sector	Private (5 clinics)	18 (18.37%)
	Public (21 clinics)	80 (81.63%)
Location	Urban	78 (79.59)
	Rural	20 (20.41)

*

Post / Position	Professional Nurse	75 (76.53%)
	Enrolled Nurse	21 (21.43%)
	Other	2 (2.04%)
Age categories	25-34	23 (24.21%)
	35-44	32 (33.68%)
	45+	40 (42.11%)
***Age**	Mean	41.87
	Median	43.17
	Range	24.74 – 69.27
Gender	Male	9 (9.18%)
	Female	89 (90.82%)
Time administering EPI vaccines	<1 month	3 (3.06%)
	1 month – 1 year	12 (12.24%)
	1-5 years	36 (36.73%)
	>5 years	47 (47.96%)
EPI Training	Yes	76 (77.55)
	No	21 (21.43)
	Uncertain	1 (1.02)
Time since last training	< 1month	3 (3.06)
	1 month – 1 year	18 (18.37)
	1-5 years	37 (37.76)
	>5 years	18 (18.37)
	No & Uncertain	22 (22.45)
Method of learning multiple injections	Self taught/ Observation	8 (8.16)
	Taught by Colleague	15 (15.31)
	Training by supervisor / site mentor	16 (16.33)
	Written Instructions	5 (5.10)
	Training session with vaccinators from other health facilities	15 (15.31)
	Formal training course	37 (37.76)
	Other	2 (2.04)
When learnt to give multiple injections	< 1 month	1 (1.02)
	1 month – 1 year	13 (13.27)
	1 -5 years	47 (47.96)
	>5 years	37 (37.76)

Description of age as a continuous variable

Table 10: Vaccinator Practice and Experience (N = 98)

Variable	Categories	n (%)
Use of standard written protocol for multiple injections for immunizations	Yes	95 (96.94)
	No	3 (3.06)
Copy of protocol/ guideline seen	Protocol in immunization room	83 (87.37)
	Protocol in facility / other room	10 (10.53)
	No protocol seen	2 (2.11)
Assistance of another staff member needed to hold baby to give multiple injections	Always	4 (4.08)
	Often	1 (1.02)
	Sometimes	10 (10.20)
	Seldom	8 (8.16)
	Never	75 (76.53)
Importance of providing information to caregivers about multiple immunizations	Very important	97 (98.98)
	Somewhat important	1 (1.02)
	Important	0 (0.00)
	Slightly important	0 (0.00)

	Not important at all	0 (0.00)
Frequency of explaining the reasons for multiple injections to caregiver	Always	54 (55.10)
	Often	26 (26.53)
	Sometimes	16 (16.33)
	Seldom	2 (2.04)
Main source of information about multiple immunizations for caregivers	Pamphlets	9 (9.18)
	Posters	13 (13.27)
	Nurses discuss RTHC	27 (27.55)
	Health promoters	38 (38.78)
	CHWs	8 (8.16)
	Other	3 (8.6)

Table 11: Vaccinator Practices – Observed (N= 129 observations)

Variable	Categories	n (%)
Province	KwaZulu Natal	12 (9.3)
	Western Cape	117 (90.7)
Sector	Private	15 (11.6)
	Public	114 (88.4)
Greeted and made eye contact with carer	Yes	120 (93.0)
	No	9 (7.0)
Made friendly contact with infant	Yes	112 (86.8)
	No	17 (13.2)
Reassured/ encouraged the caregiver	Yes	89 (69.0)
	No	40 (31.0)
Explained the importance of the infant being fully immunized	Yes	69 (53.5)
	No	60 (46.5)
Explained the procedure clearly	Yes	84 (65.1)
	No	45 (34.9)
Explained what was expected of the mother during the procedure	Yes	91 (70.5)
	No	38 (29.5)
Provided answers the caregiver seemed satisfied with	Yes	41 (31.8)
	No	5 (3.9)
	Not applicable	83 (64.3)
Infants position during immunization	Baby lying on bed	19 (14.7)
	Baby on caregivers lap	108 (83.7)
	Another health worker holding the baby	1 (0.8)
	Other	1 (0.8)
Did the mother seem upset by the 3rd injection	Yes	27 (20.9)
	No	102 (79.1)
Reassured the mother during the procedure	Yes	80 (62.0)
	No	49 (38.0)
Provide counseling about common side effects	Yes	26 (20.2)
	No	103 (79.8)
Informed the caregiver when to return for the next immunization	Yes	66 (51.2)
	No	63 (48.8)
Administered all vaccines due at this	Yes	122 (94.6)

visit	No	7 (5.4)

Table 12: Acceptability of multiple injections to vaccinators (N=98)

Variable	Categories	n (%)
Level of concern about giving multiple injections at one visit	Very concerned	24 (24.49)
	Somewhat concerned	8 (8.16)
	Concerned	9 (9.18)
	Slightly concerned	13 (13.27)
	Not concerned at all	44 (44.90)
Specific concerns about giving 3 immunization injections at on visit	Side effects	6 (11.11)
	Crying & pain	32 (59.26)
	Difficulty holding child	2 (3.70)
	Caregiver not coming back	10 (18.52)
	Don't know enough about why Immunization given	3 (5.56)
	Other (Parent objection)	1 (1.85)
Too many immunisation injections at one visit?	2 injections	2 (2.04)
	3 injections	49 (50.00)
	>3 injections	45 (45.92)
	Uncertain	2 (2.04)
Frequency of caregivers of babies (6 weeks old) expressing unhappiness about multiple injections	Always	20 (20.41)
	Often	36 (36.73)
	Sometimes	22 (22.45)
	Seldom	12 (12.24)
	Never	8 (8.16)
Frequency of caregivers of babies (older than 6 weeks) expressing unhappiness about multiple injections	Always	7 (7.14)
	Often	12 (12.24)
	Sometimes	23 (23.47)
	Seldom	27 (27.55)
	Never	29 (29.59)

Table 13: Acceptance of multiple injections to vaccinators (N = 98)

Variable	Categories	n (%)
Advised the caregivers to rather bring the child for extra visits, so that they get fewer immunizations at each visit	Always	7 (7.14)
	Often	3 (3.06)
	Sometimes	1 (1.02)
	Seldom	8 (8.16)
	Never	79 (80.61)

Table 14: **Comparison of vaccinators by Province**

Variable	Category	Province		Chi-square P-value
		KwaZulu Natal	Western Cape	
Sector	Private	8	10	0.196
	Public	23	57	
Location	Urban	26	52	0.475
	Rural	5	15	
Post/position	Professional Nurse	18	57	0.013

	Enrolled nurse	12	9	
	Other	1	1	
Age categories	< 34	9	14	0.617
	34-45	11	21	
	>45	11	29	
Gender	Male	2	7	0.524
	Female	29	60	
Nursing experience	<1 year	1	2	0.724
	1-5 years	6	18	
	>5 years	24	47	
EPI experience	<1 year	9	6	0.028
	1-5 years	8	28	
	>5 years	14	33	
EPI training	Yes	24	52	0.782
	No	7	14	
	Uncertain	0	1	
Frequency of explaining the reasons for multiple injections to caregiver	Always	26	28	0.002
	Often	3	23	
	Sometimes	2	14	
	Seldom	0	2	
Concern about giving multiple injections at one visit	Very concerned	10	14	<0.001
	Somewhat concerned	7	1	
	Concerned	2	7	
	Slightly concerned	7	6	
	Not concerned at all	5	39	
Maximum immunization injections at one visit	2 injections	1	1	0.505
	3 injections	18	31	
	>3 injections	12	33	
	Uncertain	0	2	
Advised caregivers to bring child for extra visits for fewer immunisations at each	Always	7	0	<0.001
	Often	2	1	
	Sometimes	1	0	
	Seldom	4	4	
	Never	17	62	
Observations				
Counselled mother about side effects	Yes	5	21	0.051
	No	7	96	
Informed caregiver when to return for next appointment	Yes	10	56	0.019
	No	2	61	
Administered all vaccines due at visit	Yes	11	111	0.641
	No	1	6	

Table 15: **Comparison of vaccinators by sector**

Variable	Category	Sector		Chi-square P-value
		Private	Public	
Province	KwaZulu Natal	8	23	0.196
	Western Cape	10	57	

Post/position	Professional Nurse	17	58	0.030
	Enrolled nurse	0	21	
	Other	1	1	
Age categories	< 34	5	18	0.068
	34-45	2	30	
	>45	11	29	
Gender	Male	1	8	0.555
	Female	17	72	
Time working in EPI	< 1 year	1	14	0.019
	1-5 years	3	33	
	>5 years	14	33	
EPI training	Yes	17	59	0.163
	No	1	20	
	Uncertain	0	1	
Frequency of explaining the reasons for multiple injections to caregiver	Always	11	43	0.013
	Often	4	22	
	Sometimes	1	15	
	Seldom	2	0	
Concern about giving multiple injections at one visit	Very concerned	3	21	0.686
	Somewhat concerned	1	7	
	Concerned	3	6	
	Slightly concerned	3	10	
	Not concerned at all	8	36	
Maximum immunization injections at one visit	2 injections	0	2	0.806
	3 injections	9	40	
	>3 injections	9	36	
	Uncertain	0	2	
Advised caregivers to bring child for extra visits for fewer injections at each	Yes	2	9	0.987
	No	16	71	
Observations				
Counselled mother about side effects	Yes	13	13	<0.001
	No	3	100	
Informed caregiver when to return for next appointment	Yes	12	54	0.024
	No	4	59	
Administered all vaccines due at visit	Yes	14	108	0.822
	No	1	6	

Table 16: Acceptance of multiple injections to vaccinators by years of experience administering EPI

		Number of injections considered too many at a single visit				Fisher's exact
	Categories	Two	Three	More than three	Uncertain	
Vaccinator EPI experience	0-1 year	0	8	7	0	0.843
	1-5 years	0	19	17	0	
	> 5 years	2	22	21	2	

Summary: 2015 Tanzania Multiple Injections Study: Provider and Caregiver Survey In Preparation for IPV Introduction

In preparation for IPV introduction and the switch from tOPV to bOPV, a survey was conducted in Tanzania in late 2014/early 2015 to assess perceptions of national and district health managers, service providers, and community members on multiple injections for immunization. The study used a qualitative methodology approach; in-depth interviews were conducted with health sector staff members and focus group discussions were conducted with community members. In each location, 3 focus group discussions were held: one with community leaders, one with fathers and one with mothers/female caregivers. Data collection occurred in four regions of Tanzania Mainland and 2 regions of Zanzibar. A total of 18 interviews with health managers, 36 in-depth interviews with healthcare providers and 36 focus group discussions with 8-12 community members each were conducted across the 6 locations.

With regard to number of injectable vaccines administered at a single visit, most service providers (74%) reported that the current vaccination schedule posed no problem while 13% said that the schedule had too many injections. When asked about the number of injections they thought was appropriate to be administered at once, 46% of all providers reported that up to 2 injections, and 41% reported that 3 injections, would be an appropriate number. The most frequently mentioned challenge to introduction of IPV was presumed parental concerns (59%), followed by storage of vaccines (13%).

When providers were asked whether an additional injection will affect their work, most (74%) reported no effect. When service providers were asked if they foresaw any benefit of multiple injections, 59% said multiple injections protect children, 13% said these will reduce the number of visits and 13% said multiple injections increase efficiency, while 15% did not feel that multiple injections would have any benefit. Perceived disadvantages of introducing multiple injections as mentioned by service providers include: additional pain (18%), a possible drop in immunization coverage due to multiple injections (15%), increased resource requirements such as additional syringes, and an increased number of staff (5%). However, most (61%) did not mention any disadvantage.

Most service providers (82%) said they were comfortable with administering three injections at the same visit, and only 16% were not comfortable with administering three injections at once. 36% of all interviewed service providers had administered up to two injections, and 44% had administered up to three injections, by the time of the survey. When asked about how many injections they would be comfortable with administering at one time, about half of providers (51%) said up to three injections, 31% said up to two injections, and 16% said they would be comfortable with administering more than three injections during the same visit. Providers recommended several messages for introducing IPV. The most frequently mentioned message would explain why introducing IPV was important (36%), followed by information about the safety of multiple injections (13%) and assurance of the IPV vaccine's safety (10%).

Most parents and community leaders were accepting of multiple injections and provided a number of reasons: a 14 week-old child cannot experience fear of injections, reduced cost and time as the parent and the child will have fewer clinic visits, a child receives a full dose as he/she cannot vomit or spit it out, the mother will have time to rest as she is likely to have fewer vaccination visits, and the child gets immunized at a youngest appropriate age.

While the pain caused by three simultaneous injections was an expressed concern, the study revealed multiple situations where children already receive three or more injections including: when children receive BCG late with PCV1 and Penta1 and when older, unvaccinated children of migrant populations present for vaccination services and often must receive three injections.

For successful implementation of IPV in the context of an increased number of injections, the following are recommended: 1) Conduct comprehensive community education and mobilization, 2) build capacity of service managers to ensure awareness of IPV introduction, 3) train service providers to ensure they are comfortable with providing multiple injections and 4) package vaccines into smaller, multi-dose (or single-dose) vials to ensure no child is turned away for vaccination.

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Experiences with provider and parental attitudes and practices regarding the administration of multiple injections during infant vaccination visits: Lessons for vaccine introduction☆

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ABSTRACT

Introduction: An increasing proportion of childhood immunization visits include administration of multiple injections. Future introduction of vaccines to protect against multiple diseases will further increase the number of injections at routine immunization childhood visits, particularly in developing countries that are still scaling up introductions. Parental and healthcare provider attitudes toward multiple injections may affect acceptance of recommended vaccines, and understanding these attitudes may help to inform critical decisions about vaccine introduction.
Methods: We conducted a systematic review of the literature to examine factors underlying reported parental and healthcare provider concerns and practices related to administration of multiple injections during childhood vaccination visits.
Results: Forty-four articles were identified; 42 (95%) were from high income countries, including 27 (61%) from the USA. Providers and parents report concerns about multiple injections, which tend to increase with increasing numbers of injections. Common parental and provider concerns included apprehension about the pain experienced by the child, worry about potential side effects, and uncertainty about vaccine effectiveness. Multiple studies reported that a positive provider recommendation to the parent and a high level of concern about the severity of the target disease were significantly associated with parental acceptance of all injections. Providers often significantly overestimated parental concerns about multiple injections.
Discussion: Providers may play a critical role in the decision for a child to receive all recommended injections. Their overestimation of parental concerns may lead them to postpone recommended vaccinations, which may result in extra visits and delayed vaccination. More research is needed on interventions to overcome provider and parental concern about multiple injections, particularly in developing countries.
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1. Introduction

In 1974, when the World Health Organization (WHO) created the Expanded Program on Immunization, six antigens and up to eight vaccine doses (some vaccines require multiple doses) were included in the recommended childhood vaccination schedule. By 2012, the WHO recommendations had increased to 11 antigens administered as up to 21 vaccine doses [1]. The availability of funding for vaccine introduction for low- and middle-income countries through the GAVI Alliance and other mechanisms will soon enable more countries to introduce all WHO-recommended vaccines [2]. Introduction of pneumococcal conjugate vaccine (PCV) will reduce child mortality worldwide, and the introduction of inactivated poliovirus vaccine (IPV) in all countries is a critical component of the Global Polio Eradication Initiative endgame strategy [3]. These introductions will also increase the number of injections at vaccination visits in nearly all countries [2]. This trend will continue as vaccines currently being developed for malaria, tuberculosis and other diseases are licensed and introduced [2–4].

☆ *Disclaimer*: The findings and conclusions in this report are those of the authors and do not necessarily represent the official positions of the World Health Organization or the U.S. Centers for Disease Control and Prevention.

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An important consideration in the introduction of a new injectable vaccine is the increase in the number of recommended injections at a single vaccination visit. The universally endorsed practice of simultaneous administration of all recommended vaccines improves timeliness, ensures protection at the earliest possible age, and maximizes efficient use of finite health sector resources, which is particularly important in low- and middle-income countries [5,6]. However, since many of these countries have not yet introduced all WHO-recommended vaccines, little is systematically documented about healthcare provider and parental attitudes and practices toward vaccination visits with increased numbers of injections in these locations. Countries having well-documented provider and parental experiences with multiple injections may provide important information to help low- and middle-income countries prepare for an increase in the recommended number of injections given at a vaccination visit. To better understand the determinants of provider and parental attitudes about multiple injections, we conducted a systematic review of the literature. Our aim was to identify studies of parental and provider attitudes and practices regarding vaccination visits with multiple injections and factors associated with these attitudes and practices, and to consider strategies to increase acceptance.

2. Methods

2.1. Search strategy

We searched 29 databases for English, French and Spanish language articles (Table 1). Our search filters combined terms (and their derivatives) specific to vaccination, multiple injections (and synonyms), health care provider and parental (or other caregiver) practices, attitudes or beliefs. We identified gray literature reports and working papers related to multiple injections through discussions with immunization experts at UNICEF, WHO and the US Centers for Disease Control and Prevention (CDC), and examined references in identified articles to identify additional studies. We initially reviewed titles and abstracts of identified articles to determine if papers met the eligibility criteria. Articles that appeared to meet the eligibility criteria were fully read to ensure eligibility to be included in the systematic review process.

2.2. Eligibility criteria

We included papers that described findings from primary research in a setting of childhood vaccination services and assessed one or more of the following: (a) provider or parental attitudes or practices (or both) related to simultaneous administration of multiple injections; (b) provider or parental practices regarding administration or acceptance of multiple injections following recent addition of a new injectable vaccine to an existing vaccination visit; or (c) strategies for overcoming provider or parental concerns about administration of multiple injections. Studies could be from any country, published from January 1970 through January 2014. For the purposes of this analysis, we refer to all caregivers as parents.

2.3. Article review and analysis

We used a standardized data collection form to systematically abstract information from each article, including study rationale, country, vaccinations offered, sample size, data collection methods, and key findings and recommendations. We synthesized the abstracted information, identifying common areas of concern about multiple injections for providers and parents, and factors related to these concerns and their impact on vaccine coverage and delay; and summarized both tested and proposed interventions to overcome resistance to multiple injections.

Table 1
Keywords and data sources used for a systematic review of parental and health care provider attitudes and practices related to adding injections to childhood immunization schedules using literature from 1970 to 2014.

Keywords used singly or in combination	Literature databases used	Websites visited and organizations contacted
Acceptance	Access UN	www.basics.org
Added	AccessScience	www.searchbeta.bl.uk
Attitude[a]	AGRICOLA	www.care.org
Barrier[a]	Bioline International	www.fhi.org
Behavior[a]	BioMed Central	www.filariasis.org
Caregiver[a]	BIOSIS	www.gavialliance.org
Combination	CAB Abstracts	www.greynet.org
Compliance	CHID Online	www.hki.org
Concomitant	CINAHL	www.ifrc.org
Doctor[a]	Cochrane Library	www.msh.org
HBV	CSA-Illumina Databases	www.nyam.org/library/greylitorgs.shtml
Health worker[a]	Dissertation Abstracts	www.paho.org
HiB	EMBASE	www.path.org
Immunization[a]	Expanded Academic ASAP	www.pathfind.org
Infant	Global Health	www.psi.org
Injection[a]	IBSS	www.redcross.org
Vaccination[a]	IndMed	www.savethechildren.org
Multiple	LexisNexis Academic	www.savethechildren.org.uk
Simultaneous	LILACS	www.trachoma.org
Additional	MEDLINE	www.un.org
Pain	PAIS	www.undp.org
Parent[a]	POPLINE	www.who.int/library
Physician[a]	Population Index	Centers for Disease Control & Prevention
Pneumococcal	Proquest Research Library	UNICEF
IPV	PubMed	World Health Organization
Meningococcal	SIGLE	
Hepatitis B	UNDP Project Reports	
Practice	Web of Science	
Provider[a]	WHOLIS	
Schedule		
Vaccine[a]		
Sequential		
Combo		
Concern		

[a] Keyword search included singular and plural version of word.

3. Results

3.1. General characteristics of included publications

Among 218 articles identified by the initial review of abstracts and titles, 44 met the final inclusion criteria and were reviewed (Fig. 1). Forty-two (95%) of these were from peer-reviewed journals and 2 (5%) came from gray literature sources (Table 2). Only two (5%) studies were from low- or middle-income countries (Rwanda and Ukraine); whereas 27 (61%) were conducted in the United States, 6 (14%) in Canada and 6 (14%) in other high-income countries, including one seven-country survey (Table 2).

In four (9%) studies, investigators reviewed vaccination records, in 37 (84%) they conducted interviews (14 [32%] with providers only, 15 [34%] with parents only, and 8 [18%] with both), and in 4 (9%) they evaluated strategies to increase acceptance of multiple injections. Specific injectable vaccines were reported to have been recently introduced in 26 (59%) studies, including PCV ($n=7$); IPV ($n=4$); PCV and IPV ($n=1$); PCV, influenza and varicella vaccines ($n=1$); hepatitis B vaccine (HepB) ($n=7$); meningococcal C vaccine (MenC) ($n=3$); HepB and MenC ($n=1$), *Haemophilus influenzae* type b vaccine (Hib) ($n=1$) and a switch from whole-cell diphtheria–tetanus–pertussis (DTP) vaccine to acellular (DTaP)

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Table 2
Summary of studies analyzing provider and parental attitudes and practices regarding administration of multiple injectable vaccinations during a single routine infant vaccination visit, 1970–2014; by study type and year.

Ref.	Study year	Country	Study question	New vaccine(s)	Sample	Key findings
Healthcare provider-only studies						
[46]	1991	USA	Assess supply-side risk factors for non-vaccination	NA	175 HCPs	Identified reason for delayed vaccination was lack of simultaneous administration of multiple injectable vaccines
[11]	1992	USA	Assess provider attitudes for administering vaccinations	NA	1565 HCPs	HCPs who did not want to give all injections were concerned about infant pain, side effects, parental objections, overloading immune system
[15]	1992	USA	Post vaccine introduction assessment	HepB	476 HCPs	28–44% of physicians had not adopted new vaccine recommendation due to belief of too many injections in one visit
[16]	1992	USA	Assess provider attitudes and practices regarding new vaccination	HepB	368 HCPs	HCP belief in severity of disease determined likelihood of adding additional injection
[18]	1992	USA	Post vaccine introduction assessment	HepB	153 HCPs	37% of HCPs were opposed to infant receiving 3 injections in one visit
[7]	1993	USA	Assess provider attitudes and practices regarding vaccination	NA	62 HCPs	HCPs who did not want to give all injections were side effects, parental objections; private HCPs more concerned than public HCPs.
[20]	1994	USA	Assess provider attitudes and practices for administering vaccinations	NA	1241 HCPs	HCPs who did not want to give all injections were concerned about side effects, parental objections, overloading immune system
[17]	1998	USA	Post vaccine introduction assessment	IPV	263 HCPs	The choice of OPV versus IPV was significantly influenced by perceived risk of vaccine-associated paralytic paralysis from OPV and increased number of injections
[40]	1998	USA	Assess provider practices after introduction of a new injectable vaccine	IPV	673 HCPs; 8779 records	23% of HCPs almost always offered to defer a dose when 3 injections were due and 34% offered to defer a dose when 4 were due
[14]	2000	USA	Post vaccine introduction assessment	PCV	306 HCPs	20% of HCPs deferred PCV because of concern administering four injections in one visit
[12]	2000	USA	Assess HCP attitudes regarding MI in a single visit	PCV, IPV	232 HCPs	HCP factors related to adopting new PCV recommendations include comfort with 4 injections at one visit, low concern about any adverse events with 4 injections, belief in PCV effectiveness
[13]	2001	USA	Post vaccine introduction assessment	PCV	694 HCPs	95% of HCPs who adopted PCV recommendations within first year administer 4 or more injections at 2-month visit
[24]	2001	USA	Post vaccine introduction assessment	PCV	426 HCPs	After PCV introduction, 39% of HCPs deferred at least 1 injection to later visits and 15% added an additional new visit
[21]	2001	USA	Assess prevalence of injections being deferred based on number of injections due at a single visit	PCV	32 HCPs; 858 records	The rate of deferral of injections was associated with the number of injections due in a visit. Not deferring was the strongest predictor of up-to-date vaccination by 12 and 24 months of age
Parent-only studies						
[45]	1989	USA	Assess parental attitudes regarding vaccination and compare to vaccination status	NA	557 parents	Parental concern about safety of receiving ≥1 injection a single visit inversely related to child's vaccination status i.e. those not vaccinated had higher belief in multiple injections
[28]	1992	USA	Assess parental attitudes regarding MI in a single visit	NA	281 parents	91%, 51% and 41% of parents approved of 2, 3, and 4 injections, respectively, in a single visit
[37]	1995	USA	Assess parental willingness-to-pay values to allow MI in a single visit	NA	1059 parents	Vaccination delay by age 12 months occurred where health care providers (HCPs) offered to defer receiving ≥1 injection versus HCPs who did not offer to defer any injections
[10]	1996	USA	Assess parental attitudes regarding vaccination, including MI in a single visit	IPV, DTaP	227 parents	During introduction of IPV, majority of parents choose IPV over OPV because concern about more severe side effects of OPV was higher than concern about more injections with IPV
[37]	1997	USA	Assess parental preferences for outcomes associated with vaccination using willingness to pay values	NA	206 parents	Parents placed a higher value on avoiding severe fever, disease or pain from vaccination than on reducing the number of injections in a single visit
[47]	1998	Canada	Assess reasons for vaccination delay within context of multiple injection visits	NA	696 parents	Completely vaccinated infants by 24 months of age were significantly more likely to receive all injections simultaneously as recommended compared to incompletely vaccinated infants
[36]	1999	USA	Assess parental attitudes regarding MI in a single visit using a willingness to pay economic trade-off model	NA	294 parents	Strong parental preference to limit the number of injections per visit

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Table 2 (*Continued*)

Ref.	Study year	Country	Study question	New vaccine(s)	Sample	Key findings
[42]	1999	Canada	Post vaccine introduction assessment (Hepatitis B vaccine)	HepB	255 parents	After vaccine introduction, 9.5% of children did not receive the recommended multiple injections in a single visit but instead received them separately. Main factor why they were not received simultaneously was due to HCP concern about too many injections in a single visit
[29]	2002	USA	Assess parental perceptions regarding vaccine safety	NA	7810 parents	58% of parents preferred four injections in a single visit versus separate visits. There was no difference in infant vaccination status between parents who preferred one option over the other
[41]	2002	Canada	Post vaccine introduction assessment	HepB	487 parents	Parents who reported they received a positive HCP recommendation for all injections in a single visit were significantly more likely to have an infant vaccinated with HepB
[31]	2004	The Netherlands	Post vaccine introduction assessment	HepB, MenC	283 parents	If a visit had 3 or 4 injections in a single visit instead of 1–2, then 73% and 87%, respectively, of parents would not allow all injections to be given in one visit. Parents attitudes depended on the perception of the effectiveness of the vaccine
[32]	2004	Germany	Assess parental attitudes toward new vaccinations	NA	6025 parents	56% of parents would accept administration of >1 injection in a single visit. HCPs were the most important source of vaccine information for the parent
[33]	2004	United Kingdom	Assess parental attitudes regarding vaccination, including MI in a single visit	NA	859 parents	Parents who perceived high severity of disease were more likely to accept all recommended injections in one visit
[30]	2005	Belgium	Assess parental attitudes regarding MI after vaccine introduction	PCV, IPV	1347 infants; 1315 adolescents	10% of parents would allow 3 injections per visit, 51% of parents would allow 2 injections and 20% would allow only 1 injection per visit. 65% of parents who said they would only allow 1 injection had actually previously allowed their child two received 2 injections in one visit
[34]	2006	Canada	Assess parental attitudes and practices regarding MI before versus after multiple vaccine introductions	PCV, InfV, VarV	1347 infants; 1315 adolescents	Before introduction, 28% of the group of parents would allow 3 injections in one visit; after introduction, 36% would allow 3 injections
Integrated Healthcare provider and parent studies						
[9]	1992	USA	Assess parental and provider attitudes regarding MI in a single visit	NA	215 HCPs; 193 parents	HCPs were concerned about multiple injections due to perceived increased side effects, reduced immunogenicity and concern about parents returning for subsequent visits. Parents were concerned about infant pain response, increased vaccine side effects
[8]	1993	USA	Assess parental and provider attitudes regarding MI in a single visit	NA	88 HCPs, 342 parents	HCP and parental concern about various number of injections given in one visit was similar at around 50% of surveyed groups
[27]	1996	Canada	Assess parental and HCP preferences for DTP or DTaP resulting in more injections	DTaP	400 parents, 200 HCPs	HCPs significantly overestimated the proportion of parents who would want DTP and less injections versus DTaP and more multiple injections
[19]	1997	Australia	Assess parental and provider preference for pentavalent (combined) vaccine versus separate vaccines	NA	162 parents, 154 HCPs	HCP and parents were more concerned about the higher number of side effects from DTP vaccine versus DTaP vaccine. 54% of parents and 28% of HCPs preferred three injections in one visit
[35]	2009	Rwanda	Pre-vaccine introduction assessment	PCV	16 HCPs; 50 parents	Parents were concerned about additional pain from another injection but were more concerned about disease severity. All HCPs expressed concern that parents would refuse 2 injections in one visit
[23]	2008	Ukraine	Post vaccine introduction assessment (Hib vaccine)	Hib	19 HCPs	Both parents and HCPs cited refusal of the new, additional injection as a barrier to introduction of the new vaccine and reason why coverage for new vaccine was lower than for existing vaccines
[22]	2011	Australia, Canada, France, Germany, Spain, Sweden, United Kingdom	Assessment of parental and HCP concerns about multiple injections	NA	2460 parents725 HCPs	Factors governing parental decision-making include avoiding pain of child, ensure child receives all necessary vaccines and concern about severity of disease. Factors governing HCP decision include expectations of parental concern about child's discomfort and following recommended schedule

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Table 2 (*Continued*)

Ref.	Study year	Country	Study question	New vaccine(s)	Sample	Key findings
[26]	2013	USA	Assessment of parental and HCP concerns about multiple injections	NA	401 parents 105 HCPs	HCPs significantly overestimated the proportion of parents who would prefer other routes of vaccination over the injection route. Both HCPs and parents listed severity of disease as most important factor governing the decision to administer all injections in a single visit
Healthcare record review only studies						
[44]	1997	USA	Assess vaccination outcomes after introduction of a new injectable vaccine (inactivated polio vaccine) into an existing visit	IPV, DTaP	1134 records	90% of infants received 1 or 2 injections during the first two visits prior to introduction of the new injection and switch to DTaP. After introduction, 78% of infants received 3–4 injections. Coverage by 12 months of age was similar for pre and post-introduction cohorts
[39]	2002	Australia	Assess proportion of children who were administered all recommended injections at single visit	MenC	62,000 records	Infants who received all injections as recommended per visit averaged complete vaccination by 12 months of age versus 14 months of age for those who did not receive injections as recommended
[25]	2003	Australia	Assess proportion of children who were administered all recommended injections at single visit	MenC	751 records	83% of infants received 3 injections simultaneously after new vaccine introduction compared to earlier studies showing 54% of parents were concerned about 3 injections
Intervention studies						
[47]	1995	USA	Assess if differences in infant pain and parental preference exist between simultaneous versus sequential injections during vaccination	NA	46 infants	Infants who received sequential injections show no significant pain response difference compared to infants who received injections simultaneously
[50]	2004	USA	Assess analgesic properties of oral sucrose solution during infant vaccination	NA	83 infants	Infants who received oral sucrose solution between injections had significant pain reductions two minutes after solution administration compared to placebo
[51]	2008	Canada	Assess impact of providing feedback on reasons for vaccination delay	NA	10 clinics	In clinics where feedback was received that multiple injections was a challenge, the implementation of the feedback resulted in significant decreases in vaccination delay among infants
[49]	2012	United Kingdom	Assess if differences in infant pain and parental preference exist between simultaneous versus sequential injections during vaccination	NA	72 infants	Infants who received sequential injections show no significant pain response difference compared to infants who received injections simultaneously. Parents showed no difference in perception of infant distress

Definitions: HepB = hepatitis B vaccine; Hib = *Haemophilus influenzae* type-b vaccine; IPV = inactivated polio vaccine; MenC = meningococcal C vaccine; PCV = pneumococcal vaccine; DTaP = Diphtheria–tetanus–acellular pertussis vaccine; InfV = influenza vaccine; VarV = varicella vaccine; NA = not applicable; MI = multiple injections; HIC = high income country; LMIC = low or middle income country.

vaccine ($n = 1$). In 27 (61%) studies, the authors' primary objectives included assessment of provider or parental attitudes, practices, or both concerning multiple injections, whereas in the remaining 17 (39%) studies, the topic of multiple injections was a secondary component of a vaccination program assessment.

3.2. Provider attitudes and practices related to multiple injections

Six US studies from the 1990s suggested that providers were frequently reluctant to administer all recommended injections, and this reluctance was noted in six studies to increase with the number of recommended injections [7–12]. In one provider survey in the 1990s, when the US Advisory Committee on Immunization Practices (ACIP) first recommended up to 3 injections in a single visit (Fig. 2),[1] 86% of private providers believed all doses should be administered if 1–2 injections were due, whereas only 62% believed all injections should be given if more than 2 were due [7] (Table 3). Similar results were reported from other studies during the same time period: nearly all providers (86–95%) were comfortable providing 1–2 injections [7–10], 50–64% were comfortable providing 3 injections [8–10] but only 17–23% were comfortable administering 4 injections [9]. When different groups of US-based providers were surveyed in early 1990s, 80% of pediatricians and family practitioners in one study said they would administer 3 injections, but only 66% would administer four injections [11]. By 2002, when the ACIP recommended up to seven injections at a single visit (Fig. 2), a US survey found that 35–50% of providers approved of five injections but 75–80% approved of 3 injections and 70–72% approved of 4 injections [12].

Providers who were reluctant to give all recommended injections reported a variety of reasons for their reluctance. These included concern about giving too many injections [8,13–18] or perceived reactogenicity of multiple vaccines [8,10,19]; concern about possible adverse events [13,20] or previous earlier experiences with adverse events following vaccination [9,11,19]; worry about the child's experience of pain or distress when receiving multiple injections [8,9,11,13,21,22]; vaccine cost [13–15]; parental objections [20,22,23] or the possibility that the parent might not bring the child back for future vaccinations if multiple injections were given [9,22]; as well as questioning the necessity of the newly introduced vaccine [13–16,20,23]. Nine studies suggested provider concern varied by provider type; willingness to administer multiple injections was greater among pediatricians

[1] http://www.cdc.gov/vaccines/schedules/past.html

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Table 3
Summary of healthcare providers' attitudes and practices toward administration of multiple injectable childhood vaccines during a single immunization visit; studies published 1970–2014.

Study year	Attitudes and practices toward given number of injections recommended in single childhood immunization visit					Country	No. of HCPs[a]	Source
	1	2	3	4	5			
1991			80% would administer 3 recommended injections	66% would administer 4 recommended injections		USA	490	[11]
1992			72–77% reported some caregiver opposition to 3 injections in a single visit			USA	448	[15]
1992		86–100% would administer all injections if >1 are due	62–100% would administer all injections if >2 are due			USA	62	[5]
1992			60% had strong concerns about administering 3 recommended injections	80% had strong concerns about administering 4 recommended injections		USA	289	[9]
1992	8–12% believed that 1–2 injections were too many for a single visit		59–76% believed that 3 injections were too many for a single visit			USA	88	[8]
1996			11% would not administer 3 injections in a single visit			USA	1241	[20]
1998			76% usually would not offer to defer any doses when 3 injections due	52% usually would not offer to defer any doses when 4 injections due		USA	274–399	[40]
2002	95–97% would administer 1 recommended injection	97% would administer 2 recommended injections	96–97% would administer 3 recommended injections	89–90% would administer 4 recommended injections	59–69% would administer 5 recommended injections	USA	232	[12]

[a] Number of healthcare providers (HCPs) surveyed in study.

than family practitioners [14,15,18,20,31], public clinic providers than private providers [7], and younger or more recently trained providers than older providers [9,11,24].

Provider concern about multiple injections was found to delay vaccine introduction or cause providers to deviate from recommended vaccination practices [13–18,24]. For example, following the recommended switch from oral poliovirus vaccine (OPV) to IPV in the US, a survey of pediatricians and family practitioners reported that those who continued to administer OPV expressed greater concern about the number of injections than did those who switched to IPV [17]. In another US post IPV-introduction survey, 23% of providers often deferred 1 injection when three were due and 34% deferred 1 injection when four were due [32], suggesting that providers' likelihood of deferring recommended vaccines

Table 4
Summary of parents' attitudes toward administration of multiple injectable childhood vaccines during a single immunization visit; studies published 1970–2014.

Study year	Potential acceptability of given number of injections recommended in single childhood immunization visit					Country	No. of parents[a]	Source
	1	2	3	4	5			
1992			71% believed 3 injections were too many for a single visit			USA	342	[8]
1992	31% had strong concerns about a single injection		41% had strong concerns about 3 injections			USA	193	[9]
1992		91% approved of 2 injections	58% approved of 3 injections	42% approved of 4 injections		USA	281	[28]
1996		86% were comfortable with infant receiving 2 to 3 injections		26% were comfortable with 4 injections		USA	227	[10]
1996			54% approved of 3 injections			Australia	162	[19]
2001				58% were comfortable with 4 injections		USA	7810	[29]
2005	100% approved of 1 injection	82% approved of up to 2 injections	14% approved up to 3 injections	6% approved up to 4 injections	5% approved of unlimited injections	Belgium	1347	[30]
2006	34% preferred only 1 injection	91% preferred 2 or less injections	9% approved of 3 or more injections	2% approved of 4 or more		United Kingdom	796	[33]

[a] Number of parents surveyed in study.

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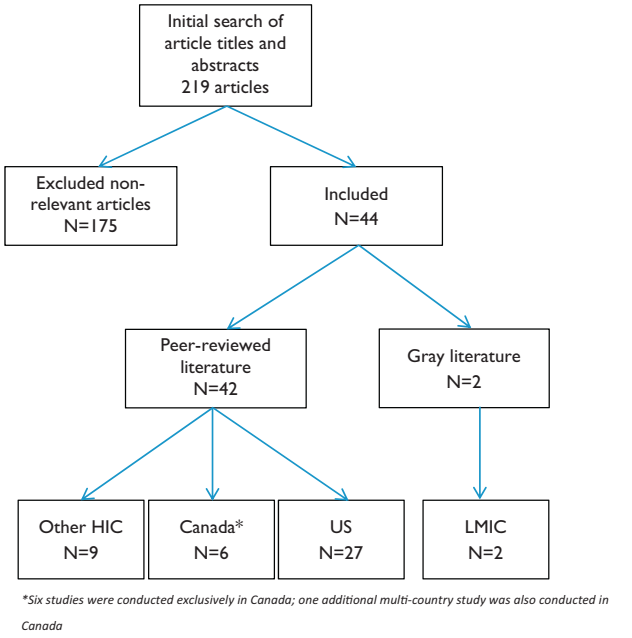

Fig. 1. Outcome of initial search and review of articles referencing provider or parental attitudes or practices regarding multiple injections. *Six studies were conducted exclusively in Canada; one additional multi-country study was also conducted in Canada

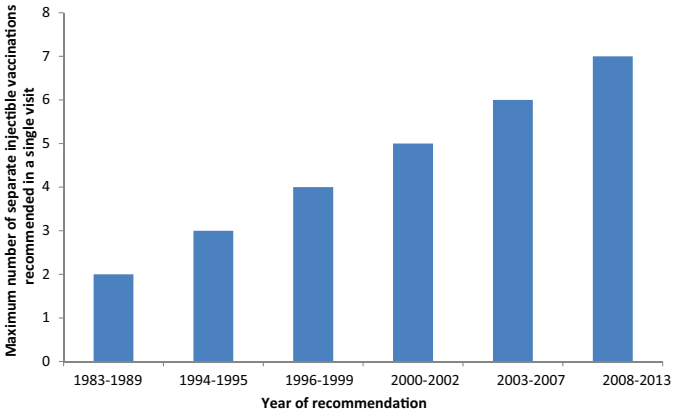

Fig. 2. Maximum number of injectable vaccinations recommended in a single pediatric visit in the United States, based on Advisory Committee on Immunization Practices (ACIP) recommendations, 1983–2013.

increased with the number of recommended injections. Providers who did not administer all recommended injections at one visit described a number of alternative delivery strategies, including deferral of one or more injections to later scheduled office visits [14,18,20,24], creation of an additional visit to administer deferred vaccinations [15,18,24,25], or increased use of combination vaccines [14].

Providers who complied with new vaccine introduction recommendations, on the other hand, were more likely than those who did not to believe the newly introduced vaccine was highly effective [13,26] and had a lower risk of side effects than previously recommended vaccines [17,27], and to believe that one visit was more convenient and less costly than two visits [8]. These providers were also more likely to be comfortable administering multiple injections [13,16]; to have personally cared for persons with the disease prevented by the vaccine [14]; to believe that the preventable disease was severe [16,22,27]; and to have received a positive endorsement to give all recommended injections at a single visit from their medical organization, medical colleagues, or both [17,24].

3.3. Parental attitudes and practices related to multiple injections

In 1992, when a maximum of 2 injections at one visit was recommended by the ACIP1 (Fig. 2), three US studies reported that parental acceptance of 3 injections ranged from 29% to 59% [8,9,28], with one study documenting a decline in parental acceptance as the number of injections increased, from 91% accepting two, 58% accepting three, and 42% accepting four injections [28] (Table 4). In 1996, when ACIP first recommended up to five injections at a visit, a US study found that 86% of surveyed parents approved of 2–3 injections, while 26% approved of four injections [10]. And in 2001, when ACIP routinely recommended four or more injectable vaccines for infants, and up to seven at age 15 months, a US survey [29] found that 58% of parents permitted their child to receive four injections at one visit, while 41% preferred to defer some doses.

In studies from multiple high-income countries [19,22,30–33], the maximum number of injections that the majority of interviewed parents were comfortable approving in a single visit corresponded to official country recommendations. For instance, in three European studies, 82% and 91% of parents in Belgium [30] and the UK [33], respectively, approved of one to 2 injections; in both countries, the maximum of injections in a single visit during the time of the survey was 2 injections. However, only 14% (Belgium), 9% (UK), and 13–27% (the Netherlands [31]) of parents approved of three or more injections, which was beyond existing recommendations during the time of the studies. Similarly, in a multi-country survey conducted in 2012 in Australia, Canada and five European countries [22], 70% of parents were most comfortable with either the officially recommended 2 injections in a visit or the number the provider recommended. Parental preferences were noted to change over time: one Canadian study found that the proportion of parents approving of ≥3 injections in a visit increased from 43% to 59% one year before compared with one year after introduction of two additional injections in a visit [34].

Reported reasons for parental concern about multiple injections included a child's potential pain [9–11,35,36], possible adverse events following multiple injections [8,10,32,34,37], and perceived stress to the immune system [27,32,34]. Parents who approved of multiple injections reportedly weighed multiple factors in the decision, including provider recommendations, perceptions of the disease severity, and vaccine effectiveness. In eight studies, parents reported that a strong provider endorsement was a key factor in their acceptance of all injections [10,22,25,37,39–42]. Six studies explored the interaction of parental perceptions of disease severity, preferences for vaccines with fewer side effects, and preferences for multiple injections [10,22,26,27,30,36]. Parental concern about disease severity and vaccine side effects outweighed parental concern about multiple injections as the parental concern about disease severity was associated with approval of all recommended injections. In one study [22], when parents were briefly educated that children were 8–25 times more likely to get the disease compared to older age groups, acceptance of the additional injection increased from 54% to 68%. In another US example [10], 92% of parents who were told about the recommended sequential IPV/OPV schedule chose IPV as the first polio vaccine for their child, and said that their concerns about OPV-associated paralytic poliomyelitis [43] outweighed their objection to an additional injection.

3.4. Comparison of provider and parental attitudes

One 1992 US study found that similar percentages of nurses (76%), physicians (59%) and parents (71%) were uncomfortable with a child receiving 3 injections [8]. However, five studies that directly

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compared provider and parental opinions about multiple injections found that their opinions often differed, and that providers frequently overestimated parental concern [9,19,22,26,27]. In one 1992 US study [9], for example, a higher proportion of providers (60%) than parents (41%) had "strong concerns" about 3–4 injections, and in a 1996 Canadian study [27], only 19% of providers predicted that mothers would willingly switch from whole-cell DTP vaccine to DTaP vaccine, if this resulted in an additional injection. However, 57% of mothers did choose DTaP because of its reduced reactogenicity compared with whole cell vaccine [44]. In a 2013 US study, 63% of providers estimated that parents would prefer a non-injectable vaccine, given the choice; however, 37% of parents stated a preference for the injection [26]. In this study, 80% of providers also predicted that parents would consider number of injections as the most important factor in approving all injections; however, 47% of parents instead cited disease prevention as the most important factor. In a 1996 Australian study, parents were more concerned about vaccine reactogenicity than multiple injections with the majority (58%) expressing a preference for DTaP alongside separate Hib and HepB vaccines (3 total injections) compared to whole-cell pentavalent vaccine (1 injection) [19]. However, provider concerns differed from the parents as 14% of providers preferred the 3 injections, including DTaP, over the pentavalent vaccine option.

3.5. Parental opinions and immunization behavior

Four studies that examined the association between parental opinions about and acceptance of multiple injections generally found little correlation [9,35,38,42]. Although all surveyed parents in two studies [9,35] said they would allow each recommended injection to be given, 31% of parents in a US study [9] and 41% of Rwandan parents [35] expressed concerns about multiple injections. In a 2002 Canadian study [42], parental concern about multiple injections was not statistically associated with children's HepB vaccination status, and a 1995 study in a US urban pediatric clinic found that 99% of children whose parents received a provider recommendation for simultaneous vaccination did receive all recommended vaccines – up to 5 injections – at the visit [38].

3.6. Multiple injections and vaccination timeliness and coverage

Two North American studies examined vaccination coverage after introduction of vaccines resulting in an increase in the number of injections [41,45]. Although a switch from OPV to IPV and introduction of DTaP increased the number of injections at two months of age from two to four, a US study [45] found no change in polio or DTP/DTaP vaccination coverage. Investigators in Canada who assessed HepB vaccination coverage six months after the vaccine was introduced at visits when DTaP–Hib–IPV combination vaccine was already given found similar DTaP and HepB coverage, and no significant correlation between multiple injections and delayed vaccination or non-vaccination [41]. Although a 2006 Canadian study found a difference in median age of vaccination among a cohort of children vaccinated after introduction of 3 injectable vaccines compared with a pre-introduction cohort, the difference (4 days) was not considered clinically significant [34].

Six studies found a correlation between concerns about multiple injections and vaccination delay [21,25,45–48]. Five reported that deferral of one or more vaccine doses because of concerns about multiple injections was associated with being incompletely vaccinated by 12, 18 or 24 months of age [14,21,25,45,48]. In a Canadian study, 85% of parents whose children were fully vaccinated by age 18 months favored 2 injections in one visit, compared with 60% of parents whose children were incompletely vaccinated [48].

3.7. Interventions to enhance acceptance of multiple injections

Four studies documented interventions aimed at increasing compliance with recommendations for simultaneous vaccination; three of these focused on efforts to reduce a child's pain in response to multiple injections [49–51]. Two trials conducted when compared parental acceptance of 2 injections administered either sequentially or by two providers administering the injections in different sites at the same time, and children's pain response [49,50]. In one trial [50], parents did not perceive a difference in child distress, while in the second [49], parents did perceive a difference and preferred the two-provider method. The independent observer measures of infant distress in both studies did not identify whether one method was better than the other. US researchers reported lower mean pain response scores following sequential injections given to children who received oral sucrose solution before vaccination compared with those who received sterile water, although pain response scores increased after each injection for both groups [51]. In the fourth study, the intervention focused on decreasing vaccination delay in Canadian clinics through use of supervisory feedback sessions with providers discussing reasons for vaccination delay [52]. In four clinics which identified multiple injections as a cause of vaccination delay, a significant decrease in vaccination delays among children was documented one year after the sessions.

3.8. Recommendations to reduce challenges with multiple injections

Development and wider use of combination vaccines was the most frequently proposed recommendation by researchers to overcome challenges associated with multiple injections [9,10,13,15,19,25,28,37,38]. Other suggested strategies for increasing provider compliance with recommendations included documenting understanding about the disease and vaccine and training to address concerns [16,25,28,38], improving provider knowledge about the safety of simultaneous vaccination [9,10,36], and ensuring articulation of a strong recommendation to the parent to vaccinate the child by the provider [9,13,19,25,27]. In one study, researchers briefly exposed parents to information about the severity of one disease, and acceptance of an additional injection increased from 54% to 68% [22].

4. Discussion

This review of the literature highlights some of the important challenges facing immunization programs in the implementation of recommendations for simultaneous administration of multiple injectable vaccines. In the United States and Canada, resistance to multiple injections among both providers and parents tended to increase as the number of recommended injections increased. However, as more immunizations were officially recommended, the maximum number acceptable to providers and parents also increased, possibly reflecting adjustment to a new "baseline" after the vaccine had been part of the routine schedule for some time. Parents weighed many factors in their decisions about accepting multiple injections, including fear of adverse reactions or impact on the immune system, pain and distress, and confidence in the vaccine, as well as the risk of acquiring the disease, and the relative benefits of some injectable vaccines (e.g., IPV vs OPV) and those with fewer antigens (e.g., DTaP vs DTP-Hib) in terms of potential side effects. Despite the influential role that providers can have in parents' decision-making process, many studies suggest

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that providers often overestimate parents' concerns about multiple injections, which may lead to delay in vaccination. Although we found little evidence that concerns about multiple injections heavily impacted vaccination coverage, studies indicated that some providers have responded to the increased number of injections by delaying and deferring infant vaccinations. Such practices may have implications for upcoming vaccine introductions in countries where vaccination timeliness may have important impacts on infant mortality and morbidity.

During the time many of the US studies in this review were conducted, introduction of several injectable vaccines nearly tripled the total number of vaccinations for children through 18 months, from seven in 1989 to 24 in 2014 [53], necessarily increasing in the number of injections administered at a single visit. However, no reviewed study examined individual-level changes in provider or parental opinions about multiple vaccine injections over time. Future longitudinal studies may help to explain how providers and parents come to accept a certain number of injections with time. Few studies directly examined interventions to overcome concerns about multiple injections, and there was little data on the effectiveness of those interventions, consistent with the general paucity of evidence regarding interventions to address vaccine hesitancy [54,55].

Parents expressed similar concerns as did providers about multiple injections; however, parental resistance was frequently overcome by their concern about the seriousness of disease itself, the inconvenience of having to return for additional injections, and most importantly, the provider's endorsement and reassurance. Parental and provider viewpoints on vaccination are known to be significantly associated [56], and surveyed parents often cite providers as a trusted source of information for decisions regarding childhood vaccination [54,56–58]. These findings, coupled with the findings that providers may overestimate the proportion of parents who will refuse multiple injections, point to the need to educate providers to explain the benefits of administration of multiple injections to parents who may initially appear reluctant, rather than offer to defer injections because of fear of parental resistance.

Apart from concern about parental refusal of multiple injections, providers cited similar reasons as parents for their own concerns, including worries about adverse reactions, discomfort and especially, questions about the need for a particular vaccine. Ensuring that providers understand the efficacy of the vaccines in question and receive education about disease severity, particularly if they have not had direct experience caring for patients with the disease, may help to overcome such challenges. In addition, providers should receive positive endorsements about multiple injections from their respective medical organizations. Specific strategies may need to be targeted toward providers who may be less likely to recommend multiple injections, including providers who have been practicing for many years.

This review had a number of limitations. Studies differed in sample size and location, and the absence of repeated measurements over time within the same population group limited the ability to measure attitude and behavior changes. A number of studies relied on convenience samples, which restricted our ability to compare findings from different studies. Additionally, many providers completed self-reporting questionnaires, which could have biased the results. Importantly, 95% of the studies were conducted in high-income countries, including 61% in the United States, which restricts our ability to generalize findings to low- and middle-income countries. Since many new vaccine introductions are or will be occurring in these countries, it is important to understand the attitudes and practices of providers and parents in these settings, so that appropriate and effective training can be developed, tested, and implemented. Other agencies who support national immunization programs but were not contacted, such as USAID, the Safe Injection Global Network or John Snow Inc., may also have unpublished literature which were not reviewed. Additional studies and publications of past experiences from low-and middle-income countries are warranted. Future studies should include parent and provider interviews, vaccination record reviews and immunization visit observations to determine both attitudes and practices related to the number of injections recommended in a single visit.

Immunizations are among the most cost-effective health interventions with estimates of an 18% rate of return by 2020 for investments to widely introduce new and under-utilized vaccines [59]. Since vaccine introductions will inevitably result in a growing number of injections and potential challenges among providers and parents, communication is needed to ensure these groups understand that administration of multiple injections has an extensive track record of both safety and acceptability [60] in multiple countries, including in developing countries where multiple injection visits have existed in the past, prior to introduction of pentavalent vaccine. Many reviewed studies identified the importance of the healthcare provider in ensuring high administration of all vaccinations during each visit. Using multiple opportunities to provide adequate preparation of healthcare providers on the topic of multiple injections may be needed, including incorporating education and role plays during pre-service and in-service trainings. Education should focus on the safety and acceptability of multiple injections as well as the potential downsides of not administering all recommended immunizations, including increased disease burden due to less timely immunization and increased costs to the health system due to increased unnecessary visits. VPD disease eradication initiatives and routine immunization funding agencies which have important roles in vaccine introduction should also be proactive in investing into research to develop and modify routine immunization education modules to incorporate information about multiple injections, including solutions which healthcare providers can use to alleviate any parental concerns. These same entities can also take a lead role in funding future research to study the magnitude and details of any issues with multiple injections in developing countries which will be useful in defining realistic solutions which can be implemented by program managers to ensure high administration and uptake of all recommended injections at each visit.

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Summary of evidence on the administration of multiple injectable vaccines in infants during a single visit: safety, immunogenicity, and vaccine administration practices

Prepared for the April 2015 SAGE Meeting

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Contents

Introduction

As new vaccines are introduced into national immunization programmes, there is an increasing need to provide clear and sound guidance to countries on how to handle the administration of multiple injectable vaccines to infants during the same immunization visit. In view of perceived hesitancy of health care workers or caretakers about accepting the administration of multiple injectable vaccines during the same visit, some national programmes are choosing various alternatives: delaying scheduled vaccinations, creating additional visits, administering doses during other visits that are not within the recommended interval between doses, or administering injections via different routes to avoid giving more than one injection in the same limb or visit. Even in the case that national programmes do not alter the schedule, apparent hesitancy by vaccinators to administer multiple injectable vaccines can pose a risk to the success of immunization programmes and may result in parents declining scheduled vaccines.

Prior to PCV being recommended for the routine childhood immunization schedule, there were few examples of EPI programs that required more than 1 vaccine in a visit. However, countries using PCV, pentavalent (DTP-HepB-Hib) and IPV vaccines are now faced with the possibility of administering multiple injectable vaccines in one visit. This issue has become more prominent in the context of the Inactivated Polio Vaccine (IPV) introduction as part of the Polio Eradication and Endgame Strategic Plan 2013-2018. Although many country EPI programmes have been administering two injectable vaccines at a visit (mainly pentavalent and PCV vaccines), the addition of the injectable IPV at 14 weeks can lead to recommendations that three injectable vaccines be administered at a single visit, which has caused concern in some countries. Although there are no specific SAGE recommendations on multiple injections in the context of administering pentavalent, PCV, and IPV in one visit, WHO has provisionally provided the following recommendations:

- IPV (non-adjuvanted) can be given intramuscularly (IM) or subcutaneously (SC), but because of reduced reactogenicity and easier administration, the WHO recommends the IM route.
- For IM injections in infants below 15 months of age, the deltoid injection site (upper arm) should not be used due to its inadequate muscle mass.
- When three IM injections are scheduled simultaneously in children under 15 months of age, it is safe and acceptable to give 2 injections in the same thigh.
- For this, the WHO recommendation is: One thigh: PCV+IPV, separated by 2.5 cm; the other thigh: DTP-HepB-Hib.

We present the evidence from both the peer-reviewed and grey literature that pertains to the recommendations on multiple injections at a single visit. Information in this document focuses on the administration of IPV, PCV, and DTP-HepB-Hib vaccines as these will be the vaccines most commonly

administered simultaneously during the same visit, once all countries have introduced IPV. Acellular-pertussis containing vaccines were not the focus of this summary as they are not often used in developing countries. However, they were included in some of our findings on adverse events following simultaneous administration of vaccinations because the studies provided relevant information for our review when such information was lacking for whole cell pertussis vaccines. We organized our findings based on four topic areas:

1. Biological Issues: Is there evidence that giving immunizations simultaneously at the same visit has the same biologic effect as when they are given alone?
2. Safety Issues: Is it safe to administer multiple injectable vaccines simultaneously? Are there any cumulative enhanced adverse effects from administering multiple injectable vaccines simultaneously?
3. Methods of Administration: What is the recommended method for administering multiple injections in a single visit?
4. Programmatic: What is the recommended practice for preparing for an immunization session at which multiple injectable vaccines will be administered?

Methods

A systematic review was conducted on the administration of multiple injectable vaccines to an infant in a single visit, and articles were reviewed for evidence on each of the following topics:

1. Non-inferiority (immunogenicity and risk of adverse events) of giving two or more injections in the same limb compared to administration in different limbs.
2. Adverse events from administration of multiple injectable vaccines in a single visit.
3. Basis for the recommendation of giving two injections 2.5 cm (1 inch) apart.
4. Suitability of using the deltoid for intramuscular injections in infants.
5. Preference of the intramuscular versus the subcutaneous route of vaccine administration.
6. Recapping procedures and preparation of multiple vaccines for single visit.

Medline (PubMed) and Embase databases were used to search for the terms indicated in Table 1. Articles were compiled in EndNote 7, all duplicate articles were removed.

Table 1. Search terms used for Medline and Embase databases*

Database	Vaccine Types	Search Terms
Medline	***Vaccine type terms (type1-12)***	Anatomic site vaccine
	Polio	Arm administration vaccine
	IPV	Arm injection vaccine
	Pneumococcal	Injection site vaccine type1-12
	PCV	Separate extremities vaccine
	Diphtheria	Separate limbs vaccine
	Tetanus	Thigh administration vaccine
	Pertussis	Thigh injection vaccine
	DTP	Vaccination site type1-12
	Hepatitis B	
	HepB	Co-administrated vaccine
	Haemophilus influenza type b	Co-administration vaccine
	Hib	Coadministrated vaccine
		Coadministration vaccine
		Coadministration vaccine type1-12

		Concomitant administered vaccine Concomitant injection vaccine Concomitant vaccine type1-12 Concomitantly administered vaccine Concurrent administration vaccine type1-12 Simultaneous administration vaccine type1-12 Multiple injection vaccine type1-12 Vaccine given in combination type1-12
Embase **Searched the following terms, using the limit for human studies, and age groups: infant (up to 1 year), child (unspecified age), preschool child (1 -6 years), school child (7-12 years)**	***All articles were filtered by type of vaccine in the title and abstract using the following terms:*** DTP Inactivated polio IPV PCV Pentavalent Pneumococcal conjugate Pneumococcal vaccine Poliomyelitis	Anatomic site vaccine Arm administration vaccine Arm injection vaccine Injection site vaccine Separate limb vaccine Separate extremities vaccine Thigh administration vaccine Thigh injection vaccine Vaccination site Coadministrated vaccine Coadministration vaccine Concomitant administration vaccine Concomitant injection vaccine Concomitant vaccine Concomitantly administered vaccine Concurrent administration vaccine Multiple injection vaccine Simultaneous administration vaccine Vaccine given in combination

**Search terms used for each database differed due to the variations in search filters for each database*

Included articles addressed administration to an infant in a single visit via intramuscular or subcutaneous injection of >1 of following vaccines: PCV, IPV, DTP-HepB-Hib. Included articles may also have addressed Japanese encephalitis, measles, rubella, meningococcal conjugate, and yellow fever vaccines. Exclusion criteria for the review were: immunocompromised and non-responding patients, vaccines administered orally or via jet injector, articles without abstracts in English or those that could not be translated, animal studies, and results presented only after a series of vaccinations, rather than after a single visit.

Due to the large number of articles found after the initial search, articles were filtered by exclusion criteria (studies conducted among HIV-infected populations, non-English articles, animal studies, vaccines that were irrelevant to the topics or experimental) and removed from the review. Of the remaining articles, four teams of two individuals reviewed unique sets of articles by title and abstract for inclusion in the full article review. Individuals reviewed titles and abstracts separately and then compared articles that fit the inclusion criteria with his or her team member, discussed any discrepancies, and reached a final consensus on whether an article should be included for full review.

For the review of full articles, 5 individuals each reviewed a unique set of articles and abstracted relevant information using a standardized Excel-based data collection tool. The inclusion and exclusion criteria for the full article review were expanded to include articles presenting data on IPV, DTP-HepB-Hib, and PCV, but excluded articles on acellular pertussis vaccines (see exceptions below for articles addressing each objective) and pain mitigation studies.

Exceptions:

- For articles pertaining to topic 1: include articles comparing data on effects of administering an additional vaccine during a visit (for example, 2 vs. 3 vaccines administered), can include administered vaccine containing acellular pertussis antigen if it is an additional vaccine, but not if it is the initial vaccine given
- For articles pertaining to topic 2: include articles comparing data on effects of administering an additional vaccine during a visit (for example, 2 vs. 3 vaccines administered), can include administered vaccine containing acellular pertussis antigen if it is an additional vaccine, but not if it is the initial vaccine given
- For objectives 3-5: include articles presenting data on 1 or more injections, can include acellular pertussis

After the full article review was completed, articles were excluded if they presented data on the dorsal gluteal as a site of vaccine administration because it is not a recommended site of administration in infants and children due to risk of injury to the sciatic nerve. [1-4] Included articles that pertained to the attitudes of healthcare providers or caregivers on multiple injections were not analyzed as part of this review; these articles were included in the section, "Summary of evidence on the administration of multiple injectable vaccines in infants during a single visit: attitudes of healthcare providers and caregivers".

Information collected in the Excel-based tool was compiled and synthesized. Results were summarized by objective and categorized into the following groups:

- Evidence of using same limb versus different limbs for multiple vaccines during a single visit
- Safety
- Methods of vaccine administration
- Programmatic issues

Included articles were reviewed for additional relevant references. In addition, individual published and grey literature reviews were conducted for topics 3-6. These individual reviews were supplemented by a review of the WHO vaccine position papers as of February 2015, requests to experts for comments, and data from vaccine package inserts on administration. More details on the methods for the individual reviews can be found in the relevant sections.

Grey Literature Review

In order to supplement the information identified during the systematic review and individual literature reviews, we conducted a grey literature review to identify additional resources that could provide more insight. The following sources were used to identify literature: greylit.org, opengrey.eu, epocoslo.cochrane.org, Google, IRIS, unicef.int, and who.int. Search terms included: simultaneous vaccination, simultaneous immunization, multiple injections, multiple vaccine injections, multiple vaccines, or multiple immunizations. Complete searches using Google, IRIS, and who.int could not be

reviewed in time for inclusion in this report; the first 40-60 search results (which can be considered the most relevant, based on search algorithms) were reviewed, however, only 5 sources were deemed relevant from the initial searches and information from these sources has been included in the summaries of evidence below. The 6th edition of the book *Vaccines,* CDC's Pink Book, and ACIP guidance was reviewed for pertinent information along with any citations that were deemed relevant.

Limitations

We were unable to review all studies that both addressed the objectives and included other types of vaccines in the routine childhood schedule besides PCV, IPV, DTP-HepB-Hib because of time constraints. Many articles and guidance documents included in this review failed to provide data or information that was directly relevant to the objectives of the systematic review. Due to the variety and number of combinations of vaccines administered simultaneously to an infant during a single visit, it was difficult to separate outcomes by type of vaccine. Very few studies addressing the objectives took place in developing countries, and there is no or limited guidance on these objectives from the ministries of health in these countries. The lack of information on the objectives addressed by this review has been noted in other sources; safety and immunogenicity studies often do not report the anatomic site of vaccine administration while frequently documenting the route of administration.[5]

Systematic Review- Overall Results

Figure 1. Number of articles included and excluded in systematic review

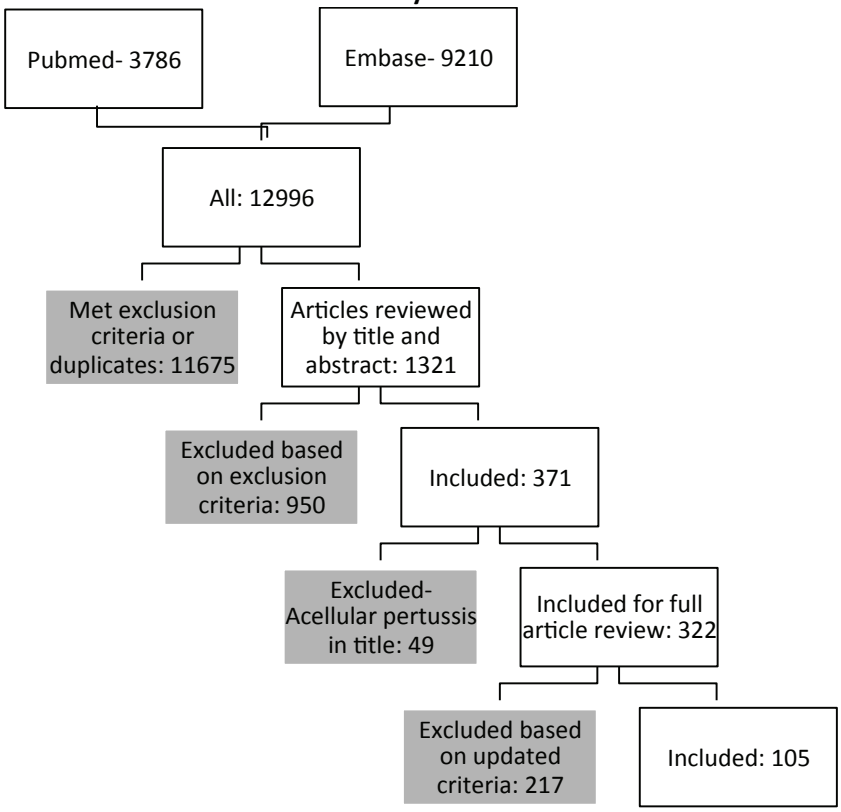

Table 2. Number of articles included after the full review by topic area and region*

	Number of Articles
Topic	
Adverse events	61
Reviews	11
Injection Technique/Prepping for Session/Other	33
WHO Regions	
AFRO	6
EMRO	1
EURO	19
PAHO	49
SEARO	3
WPRO	12
Multiple	3
Not applicable	12
Total	105

*Publication dates ranged from 1985 to 2014.

Summary: Evidence of using same limb versus different limbs for multiple vaccines during a single visit

Addresses topic- 1. Non-inferiority (immunogenicity and adverse events) of giving two or more injections in the same limb compared to administration in different limbs

The systematic review found no studies that evaluated the non-inferiority (immunogenicity and risk of adverse events) of giving two or more injections in the same limb compared to administration in different limbs for infants.

Of note is a recent study from Iro et al. on the effects on immunogenicity of administering PCV13, DTaP-IPV-Hib, and MenC conjugate vaccine to infants in the same limbs for all visits versus alternating the limbs for vaccine injection. As part of that study, the authors conducted a systematic review on the effect of administering vaccines in the same versus different limbs across visits on the immune response to infant vaccination and found no randomized trials. Only one relevant study was identified that took place among adults receiving rabies vaccine. Results from the study suggest that for some antigens in the routine infant immunization schedule, immunogenicity is not reduced, and it may even be improved, by alternating the limb of administration. The authors note that some animal studies have found that draining rather than non-draining lymph nodes have a higher number of antibody-forming cells which may account for differences in immunogenicity by site of vaccination [6-8]. [9]

WHO Recommendations

No direct evidence was identified as the basis one way or the other for the WHO recommendations listed below. Please refer to the "Safety" section for additional evidence on administering multiple injections in one limb.

- When three IM injections are scheduled simultaneously in children under 12 months of age, it is safe and acceptable to give 2 injections in the same thigh.
- For this, the WHO recommendation is: One thigh: PCV+IPV, separated by 2.5 cm; the other thigh: DTP-HepB-Hib.

Summary: Safety

Addresses topic- 2. Adverse events from administration of multiple injectable vaccines in a single visit.

Methods

See "Methods" section above.

Results

Of the 105 articles that met the inclusion and exclusion criteria of the systematic review, 61 (58%) presented data on adverse events following multiple vaccine injections among infants. However, 15 of these articles were later excluded because they included vaccines not relevant to the topics of the systematic review, injection site included the dorsal gluteal site, or results were insufficiently detailed; 45 presented data on adverse events following the administration of multiple injections in the same visit versus separate visits and the addition of another vaccine to a visit for infants. Among the randomized controlled trials, the age of the study population was up through 24 months.

Number of articles presenting adverse event data by vaccine type

Vaccine type	Number of articles
DTP, DTP-containing	17 (excluding DTP-HBV-Hib vaccine)
PCV, PCV-containing	15
DTP-HBV-Hib	6
IPV	5
Other	2
Total	45

PCV

Summary: 15 studies included PCV7, PCV11, PVCV13, PCV23, or PCV-DTP-Hib vaccines along with one or more of the following vaccines: DTaP-HepB-IPV-Hib, DTaP-IPV-Hib, DTP, DTP-Hib, DTwP-HepB-Hib, HepB-Hib, HepA, HepB, Hib, MMR, OPV, varicella, or meningococcal conjugate serogroup B (4CMenB). In general, there were no significant differences in the incidence of severe or serious adverse events when a PCV vaccine was given as the additional vaccine in a multiple injection visit vs. when a PCV vaccine was not given or when PCV was administered alone versus with other vaccines [10-23]. However, the frequency of at least one type of minor local or systemic adverse events was sometimes higher in recipients who received a PCV and one or more other vaccines at a single session instead of just the other vaccine(s), although which particular minor local or systemic adverse event was more common varied across studies [13, 14, 17, 20, 21, 23]. In one study, 17 serious adverse events judged to be vaccine related occurred in participants who received DTaP-IPV-HBV-Hib, PCV7, and 4CMenB vaccine while 1 serious adverse event judged to be vaccine related occurred in participants who received only DTaP-IPV-HBV-Hib and PCV7. [24] Although PCV7 was included in the study, any difference in adverse event rates between the two groups was likely related to the 4CMenB vaccine. Of note, one study found that infant immune responses to HepB vaccine and Hib vaccine were significantly reduced and increased, respectively, when the HepB vaccine was administered in the same thigh as DTaP-IPV-Hib and concurrently with PCV7, albeit with PCV7 administered in a different thigh, vs. when the HepB vaccine was administered in a different thigh from DTaP-IPV-Hib and at a different time from PCV7 [15].

IPV

Summary: There were 5 studies identified that included IPV as one vaccination in a multiple injection session. The IPV vaccine was either administered at a separate site or in one of the following

combination products: DTaP-IPV-Hib, DTaP-IPV, or DTP-IPV. Other vaccines studied in the reviewed trials included: DTaP, DTwP, DTaP-HepB, HepB, Hib, meningococcal conjugate, BCG, yellow fever, or MMR. Overall, IPV administered in a combination product or alone was well tolerated by infants in the reviewed studies. [25-29] Two studies among Senegalese infants found no increase in adverse reactions following simultaneous administration of DTP-IPV vaccine with HepB and/or yellow fever, measles, and BCG when compared to single administration of a vaccine or simultaneous administration of non-IPV containing vaccines. [25, 26] Two infants given DTaP, IPV, Hib, PCV7, and HebB were reported to have nonfebrile seizures during a trial comparing separate but concurrent administration of each vaccine to concurrent administration of DTaP-IPV-Hib vaccine with PCV7 and HepB vaccines [27]Among recipients of either a DTaP-IPV combination product or separate administration of DTaP and IP,V large injection site swelling, of at least 50 mm in diameter, was observed; there was a similar incidence of swelling between study groups. [28]

Pentavalent

Summary: We identified 6 studies that included pentavalent vaccine (DTwP-HepB-Hib); 4 of these studies compared the pentavalent vaccine to separate but simultaneous administration of DTwP, HepB, or Hib during a single session. Other vaccines included in the two remaining studies included: measles, OPV, yellow fever, and PCV7. One study compared simultaneous administration of DTwP-HepB-Hib with PCV7 and OPV or only OPV and found no difference in reactogenicity observed among the study groups. [10] Of note, this study did observe more grade 3 swelling at the DTwP-HepB-Hib injection site than at the PCV7 injection site for all study groups. [10] In an observational study among non-randomized infants from Guinea Bissau, it was observed that the administration of pentavalent vaccine simultaneously with measles and yellow fever vaccine was associated with increased mortality. [32] However, SAGE has previously reviewed findings on non-specific effects of vaccines on childhood mortality and concluded that they neither exclude nor confirm the possibility of beneficial or deleterious non-specific immunological effects of the vaccines under study on all-cause mortality and suffer from substantial unresolved methodologic challenges. [33]

DTP

Summary: There were 17 studies identified that included DTP or DTP-HepB, including either whole-cell or acellular pertussis antigens. Other vaccines in the reviewed studies included: DTaP, DTaP-HepB-IPV-Hib, HepB, Hib, varicella, MMR, and OPV. From the articles we reviewed, we found that in general DTP given alone or in a combination product can be safely co-administered with other vaccines [34-39]; however a number of studies did indicate a higher frequency of reported local adverse events and systemic reactions from the DTP/DTP-containing vaccine compared to other vaccines. [11, 40-46] Several studies have found conflicting results on the co-administration of DTP and MMR; one trial found an association between incidents of seizure and receipt of DTP and MMR on the same day or 8 to 14 days after [47] while an analysis of data from the US's Vaccine Adverse Events Reporting System (VAERS) found no increase in serious adverse events, and similar results were found in a clinical trial. [48, 49]

Conclusion

- In general, simultaneous administration of PCV, IPV, pentavalent, and DTP vaccines with other routine vaccines was well tolerated among infants. However there were a few notable combinations of vaccines that resulted in a reported possible increase in adverse events that should not be overlooked and may need further investigation. These include: meningococcal conjugate administered with hexavalent and PCV7 vaccines, pentavalent administered with measles and yellow fever vaccines, and DTP administered with MMR. Due to the variability of the effects of the different combinations of vaccines than can be co-administered in one visit, vaccination schedules should reflect the data on adverse events and immunogenicity of each specific vaccine combination.

Summary: Methods of administration

Addresses topics-

3. Basis for the recommendation of giving two injections 2.5 cm (1 inch) apart.
4. Suitability of using the deltoid for intramuscular injections in infants.
5. Preference of the intramuscular versus the subcutaneous route of vaccine administration.
6. Additional information on IPV administration.

Basis for the recommendation of giving two injections 2.5 cm apart.

Methods

The search terms 'injections 2.5 cm' and 'injections 1 inch' were entered into PubMed for this search. Titles were initially screened for relevance prior to a full review of the text. Multiple injection guidance documents were reviewed from the Department of Health of Australia; the Public Health Agency of Canada; and the Centers for Disease Control and Prevention and the American Academy of Pediatrics in the United States.

Results

388 titles were reviewed and three abstracts reviewed, but none were found to be relevant.

Pubmed Search:

Search terms	Hits	Title/Abstract Screen	Relevant
injections 2.5 cm	324	3	0
injections 1 inch	64	0	0

The guidance documents from Australia, Canada, and the United States recommend a minimum distance of 2.5 cm or 1 inch between injections in the same limb, but we were unable to identify the evidence on which those recommendations may have been based.

Table 3. Summary of findings from guidance documents

Country	Entity	Recommendation
Canada	Public Health Agency of Canada	Use separate limbs if two IM injections are required. If more than two injections in the same limb are required, administer the two injections into the same muscle separated by at least 2.5 cm (1 inch). In cases where there is insufficient deltoid muscle mass, the anterolateral thigh can be used in children to 35 months of age.[50]
Australia	Department of Health	For infants <12 months of age: The suitable sites for this age group are the anterolateral thighs (preferred) and the ventrogluteal areas. For the routine schedule where only two vaccines are required, one can be given in each thigh. When three or four injectable vaccines are to be given at the same visit, the options are: •two injections in the same anterolateral thigh, separated by at least 2.5 cm; further IM vaccines can be given in this way in the other thigh, or •one injection into each anterolateral thigh and one injection into each ventrogluteal area (only one injection should be given into each ventrogluteal area). [51]
USA	ACIP, CDC	2011: If multiple vaccines are administered at a single visit, administer each preparation at a different anatomic site. For infants and younger children, if more than two vaccines are injected in a single limb, the thigh is the

		preferred site because of the greater muscle mass; the injections should be sufficiently separated (i.e., ≥1 inch if possible) so that any local reactions can be differentiated [52] 1994: If more than one vaccine preparation is administered or if vaccine and an immune globulin preparation are administered simultaneously, it is preferable to administer each at a different anatomic site. It is also preferable to avoid administering two intramuscular injections in the same limb, especially if DTP is one of the products administered. However, if more than one injection must be administered in a single limb, the thigh is usually the preferred site because of the greater muscle mass; the injections should be sufficiently separated (i.e., 1-2 inches apart) so that any local reactions are unlikely to overlap [53, 54].[55]
USA	HHS/CDC	Multiple Vaccinations - If multiple vaccines are administered at a single visit, administration of each preparation at a different anatomic site is desirable. For infants and younger children, if more than two vaccines are injected in a single limb, the thigh is the preferred site because of the greater muscle mass. For older children and adults, the deltoid muscle can be used for more than one intramuscular injection. The injection sites should be separated by 1 inch or more, if possible, so that any local reactions can be differentiated. Vaccines that are the most reactive (e.g., tetanus-containing and PCV) should be administered in different limbs if possible. Use of combination vaccines can reduce the number of injections. If a vaccine and an immune globulin preparation are administered simultaneously (e.g., Td/Tdap and tetanus immune globulin [TIG] or hepatitis B vaccine and hepatitis B immune globulin [HBIG]), separate anatomic sites should be used. The location of all injection sites should be documented in the patient's medical record. Healthcare practices should consider using a vaccination site map so that all persons administering vaccines routinely use the same anatomic site for each different vaccine.[1]
USA	American Academy of Pediatrics	The distance separating the injections is arbitrary but should be at least 1 inch, if possible, so that local reactions are unlikely to overlap.[56]
	WHO WPRO	"First, IPV and PCV injections should be given in one thigh, with injection sites separated by at least 2.5 centimeters. The pentavalent injection should be given in the other thigh."[57]
	WHO GPEI	"When infants need three injections during the same visit, the first two vaccine injections are given in one thigh, with injection sites separated by at least 2 cm. The third injection is given in the other thigh."[58]

Conclusion

The guidance documents consistently recommended that multiple injections administered in the same limb should be separated by at least 2.5 cm (1 inch); no evidence was reported as the basis for this recommendation, but it was indicated that this distance allowed for local reactions to be differentiated by vaccine type.

Suitability of using the deltoid for intramuscular injections in infants.

Due to the specificity of this topic, a separate literature review was undertaken to ensure all accessible materials were assessed comprehensively. The methods and results presented below were supplemented by any other sources identified during the larger systematic review that were deemed relevant.

Methods
The search terms 'intramuscular injection deltoid' and 'IM injection deltoid' were entered into Google scholar and Pub Med for this search. Titles and abstracts were initially reviewed for relevance prior to a full review of the text. Literature reviews were included if they discussed intramuscular (IM) injection sites for infants or children. Primary source articles were included if their research question pertained to the immunogenicity, safety, or acceptability of immunization in different IM sites in infants or children. The references and citing articles of the reviews selected for inclusion were also reviewed for additional relevant sources.

Results
Five literature review articles and 11 clinical trials or observational studies were identified by the search. The literature reviews stated that the deltoid muscle is not well enough developed for IM injections in infants and cautioned that precise identification of the site and adequate muscle mass are crucial to avoid nerve and muscle injury [59-63].

There was agreement among the authors of the reviews that the deltoid is a small site, limiting the potential number of injections that can safely be administered in a given healthcare encounter. The recommendations for the maximum volume that could be injected into the deltoid muscle were inconsistent and ranged from 0.5ml to 2ml in adults ([61, 62, 64]). Two articles reported that 5ml is an appropriate maximum volume in the vastus lateralis [62, 64]. Lesser amounts should be used for children and individuals with underdeveloped or atrophied muscles [61, 62].

There is a lack of consensus in the literature regarding an appropriate age to begin using the deltoid muscle for IM injection. Sources cite ages from 12 to 35 months as suitable ages to start deltoid IM injections [52, 61-63]. One Canadian study compared adverse events following DTP-IPV administration in 18 month old infants at the vastus lateralis and deltoid sites; they found fewer moderate reactions and greater acceptability of the deltoid site; severe pain occurred in 30.5% of the groups injected in the thigh compared with only 8.1% of the group injected in the deltoid; children vaccinated in the thigh had decreased movement of the extremity more often than those injected in the arm; redness and swelling were observed more often after injection in the arm than in the thigh [54]. One study from China administered PCV7 and DTaP simultaneously in the left and right upper deltoids among infants at 3, 4, and 5 months and found that the majority of subjects experienced no induration/swelling or tenderness that interfered with limb movement. However the study group receiving both vaccines simultaneously had slightly more AEs compared to those receiving either vaccine alone in a single visit (52% for simultaneous vaccination versus 47% for PCV7 followed by DTaP 7 days later and 42% for DTaP only) [65]. Another study from China among infants between 2 and 5 months of age receiving Hib found no difference in local reaction rates between the deltoid and vastus lateralis, although incidence of systemic reactions was lower among the group receiving Hib at the vastus lateralis site than in the deltoid after the 3rd dose. [66]

As an alternative to the deltoid for IM injections, authors of the literature reviews recommend the vastus lateralis muscle (anterolateral thigh) for infants as muscle mass is sufficient from birth [59-64]. It is also appropriate for children receiving multiple injectable vaccines [64]. The risk of major injury was reported to be low because this area does not contain major nerves or blood vessels ([59-62, 64]). Another study from Canada on the administration of DTP and Hib among 18 month olds given in the anterolateral thigh in the first half of the study and in the deltoid for the second half found that rates of local reactions were higher when DTP-containing vaccines were given in the deltoid than when they were given in the anterolateral thigh [53].

The ventrogluteal (hip) site has been presented as a suitable alternative to the vastus lateralis for infants and young children and has a low risk of injury [59-62, 67]. Two recent randomized control trials in Brazil and Australia of vaccines administered to the vastus lateralis and ventrogluteal sites in neonates, infants, and young children found little difference in immunogenicity, safety, or acceptability [68-70]. It should be noted that the ventrogluteal site is different from the dorsalgluteal site, which is not recommended for vaccination and has a significant risk of injury.

Many of the key sources cited by these literature reviews are nursing textbooks, not peer-reviewed articles. As one article stated "it was found that 'proper' procedure was often non-research based and usually contained erroneous and/or out-of-date recommendations regarding the technique."[71] Indeed, several articles recommend routinely cleaning the skin and aspirating prior to injection, practices WHO recommends against for vaccination, though all five of the literature reviews identified are for general IM injections and may not reflect best practice for vaccinations. Another study noted that guidelines do not always provide recommendations that discuss the specifics of vaccine administration, such as the appropriate route of injection and the most suitable injection sites. [72]

Conclusion
There is inconsistency among sources on the age to begin using the deltoid for IM vaccine administration among infants; however multiple reviews have stated that the deltoid is not well enough developed for IM injection in infants. The vastus lateralis muscle and ventrogluteal site are recommended as alternative sites for IM injections as studies show that there is equal or more tolerability and equal immunogenicity at these sites.

Preference of the intramuscular versus the subcutaneous route of vaccine administration

Due to the specificity of this topic, a separate literature review was undertaken to ensure all accessible materials were assessed comprehensively. The methods and results presented below were supplemented by any other sources identified during the larger systematic review that were deemed relevant.

Methods
PubMed was used to identify articles using the following search strategy: [Subcutaneous] and [vaccine or vaccines] and [administration] and [human]. The vaccines types included: measles, DTP, PCV, pentavalent, IPV, Hib, HPV, HepB, meningococcal conjugate.

Results
Of the 27 articles identified by the search, there were 14 (52%) articles that met the inclusion and exclusion criteria. A 2008 commentary noted that the practice of intramuscular (IM) versus subcutaneous (SC) administration for vaccines has been based on tradition. This commentary summarized evidence on the routes of administration and reported that for studies which present data on these routes, the IM route is preferred over the SC route; studies included aluminum-adjuvanted, live attenuated, and non-adjuvanted/whole cell vaccines and indicated that injection site reactions were more likely with SC administration and that immunogenicity was greater with the IM route for HepA and B vaccines (including non-infant populations)[73]. A systematic review of articles included in the commentary came to the same conclusion [74]. The authors of the review also noted that there are few studies that directly compare the rate of reactions between SC and IM administration. One study cited in the review noted that IPV administered SC caused very few local reactions and that there was no difference in the frequency of local reactions between IM versus SC administration for IPV-containing vaccines [75].

A few studies presented results by a single route of administration. Among infants 2-6 month old, PCV13 was administered SC and was well tolerated and immunogenic [76]. Similarly, no serious or persistent adverse reactions resulted for infants administered Hib-combination vaccines simultaneously with diphtheria vaccines via the SC route [77]. For additional consideration, one study reported that HepB vaccine has been found to be safe and effective among infants receiving 2 micrograms or recombinant vaccine via the intradermal route[78].

Conclusion
In general, these studies found that immunogenicity is non-inferior between the SC versus the IM route for vaccine administration; however, there is more reactogenicity with the SC route (particularly with adjuvanted vaccines). Therefore the IM route is preferred with the SC route being an acceptable alternative.

Additional Information on IPV Administration

IPV may be given SC or IM per manufacturer's information and there are no clinical trials on the relative immunogenicity of one versus the other. However, IPV is frequently administered as a component of a combination vaccine, which has encouraged the administration of IPV via the IM route even when it is administered without other vaccines [79].

IPV Vaccine Package Insert Information on Administration and Adverse Events by Manufacturer

IPOL (IPV) from Sanofi Pasteur:
"The vaccine should be administered IM or SC; licensed for as young as 6 weeks of age. In infants and small children, the mid-lateral aspect of the thigh is the preferred site. Dose is 0.5 mL. From historical data on the antibody responses to diphtheria, tetanus, whole-cell or acellular pertussis, Hib, or Hep B vaccines used concomitantly with IPOL vaccine, no interferences have been observed on the immunological end points accepted for clinical protection. [Unpublished data from Sanofi Pasteur SA, [80, 81]] No data on the immunological interference between IPOL vaccine and MMR were identified by the manufacturer at the time of the insert's publication, October 2012. Based on data provided in the package insert, among US studies with IPOL vaccine, the percentage of detectable antibody for polio types 1,2, and 3 ranges from 97-100%, 100%, and 97-100%, respectively, following 2 doses administered SC versus 99%, 99-100%, and 95-99% following 2 doses administered IM. No information on adverse events was provided by the manufacturer."

IPV Vaccine from Bilthoven Biologicals:
0.5 mL dose. "The vaccine is given SC or IM. Poliomyelitis vaccine can simultaneously be administered with other vaccines on different injection locations."

Poliovac-PFS (IPV) from Serum Institute of India:
"Poliomyelitis Vaccine (Inactivated) is indicated for active immunization of infants (as young as 6 weeks of age), children and adults. Dose is 0.5 mL. Systemic adverse reactions reported in infants receiving IPV concomitantly at separate sites or combined with DTP have been similar to those associated with administration of DTP alone. Local reactions are usually mild and transient in nature. The most frequently reported side effects are reactions at the site of injection: pain, erythema, induration and systemic reactions like moderate transient fever. Other side effects are oedema that can occur within 48 hours and persist for one or two days, lympadenopathy, hypersensitivity reaction (urticaria, Quinckes oedema) in response to one of the vaccine components. Anaphylactic reactions occur very rarely. The other reactions are moderate and transient arthralgia and myalgia, convulsions, headaches, moderate and transient paresthesia occurring in the two days following vaccination. After preparation of the injection site, immediately administer POLIOVAC PFS intramuscularly or subcutaneously. In infants and small children, the mid-lateral aspect of the thigh is the preferred site. In older children and adults POLIOVAC PFS should be administered intramuscularly or subcutaneously in the deltoid area. From historical data on the antibody responses to diphtheria, tetanus, whole-cell or acellular pertussis,

Hib, or hepatitis B vaccines used concomitantly with Poliomyelitis vaccine (inactivated), no interferences have been observed on the immunological end points accepted for clinical protection."

Poliorix (IPV) from GSK:
Dose is 0.5 mL. "Poliorix™ is indicated for active immunisation from the age of 2 months against poliomyelitis. Poliorix™ is for deep intramuscular injection. Administration for infants: anterolateral aspect of the thigh; older children and adults: deltoid. No data are available on subcutaneous administration of Poliorix™. It is current practice in vaccination to coadminister different vaccines during the same session. If Poliorix is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites. In clinical studies, Poliorix™ has been administered concomitantly with D, T, P, HBV and Hib antigens. IPV can be given safely and effectively at the same time as measles, mumps, rubella, BCG and yellow fever vaccines and vitamin A supplementation."

IPV Vaccine from Statens Serum Insitut:
Dose is 0.5 mL. "The vaccine should be administered intramuscularly or subcutaneously. The age at the first dose should be at least 6 weeks. Between 1 and 10% of the vaccinees can expect to experience side effects, most frequently as reactions on the injection site, fever and general malaise. Local reaction at the injection site in the way of redness, tenderness and swelling can occur within the first 48 hours after injection and last for 1–2 days. The appearance and seriousness of the local reactions is dependent on the injection site and the route of administration. IPV Vaccine SSI can be given at the same time as other live or inactivated vaccines, including vaccines against measles, rubella, mumps, DTP, DT, TT, Td, BCG, hepatitis B, Haemophilus influenzae type b and yellow fever. Simultaneous vaccinations should be given at different injection sites."

Polprotec (IPV) from Panacea Biotec:
Dose is 0.5 mL. "From 6 weeks of age, POLPROTEC may be administered following the 6, 10, 14-week schedule, as per the recommendations of the Expanded Programme on Immunization of the World Health Organization. Administer POLPROTEC intramuscularly. Lateral aspect of the mid thigh is the preferred site in infants and small children. In older children and adults, it should be administered in deltoid area. POLPROTEC should not be administered into the buttocks due to the varying amount of fatty tissue in this region, nor by the intradermal route, since these methods of administration may induce a weaker immune response. Concomitant administration, of other parenteral vaccines, with separate syringes at separate sites, is not contraindicated. There is no historical data demonstrating interference of antibody response to Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA) and Haemophilus Type b Conjugate Vaccine (Adsorbed) IP used concomitantly with IPV on the immunological endpoints accepted for clinical protection. All systemic symptoms were mild/moderate in intensity. The incidence of each systemic symptom over all doses was similar in the comparator group. All the unsolicited AEs were mild/moderate in intensity."

WHO Recommendations

Relevant WHO Recommendations:

- IPV (non-adjuvanted) can be given intramuscularly (IM) or subcutaneously (SC) but because of reduced reactogenicity and easier administration, the WHO recommends the IM route.
- For IM injections in infants below 12 months of age, the deltoid injection site (upper arm) should not be used due to its inadequate muscle mass.

Conclusion:
The systematic review found evidence pertaining to the WHO recommendations listed above. The IPV vaccine is licensed for both IM and SC administration; however, only immunogenicity data following 2 doses of the vaccine is provided by the manufacturer and no route-specific safety information is presented. The immunogenicity data following 2 doses is similar for both routes of administration. For other vaccines, studies have repeatedly shown

that IM administration provides equal or greater immunogenicity and fewer local reactions than SC administration, with some slight variations by vaccine type. This supports the WHO's current recommendation of administering IPV via the IM route.

Regarding the use of the deltoid for IM injections among infants, there is inconsistency in the literature on the appropriate age to begin using this muscle for vaccine administration. The ages reported in the literature for use of the deltoid ranged from 12 to 18 months and have been cited in some sources as up to 3 years. Sources indicate that the deltoid muscle is not well enough developed for IM injections in infants and that the anterolateral thigh (vastus lateralis) is recommended for infants as the mass of this muscle in infants is sufficient and the risk of injury is low since there are no major nerves or blood vessels in this area. Additionally, commentaries from clinicians have brought to light that decision-making regarding use of the deltoid for vaccine administration is often not based on published recommendations. Instead, personal judgment is used to make this decision, based on other biological factors and experience [82]. Therefore, while the WHO's recommendation for using the deltoid at 12 months for vaccination is supported by the guidance identified by the review, more evidence is needed that is relevant to the safety and effectiveness of using the deltoid of infants for vaccination.

Summary: Programmatic Issues

Addresses topic- 5: Recapping procedures and preparation of multiple vaccines for single visit.

Due to the specificity of this topic, a separate literature review was undertaken to ensure all accessible materials were assessed comprehensively. The methods and results presented below were supplemented by any other sources identified during the larger systematic review that were deemed relevant.

Methods

Immunization guides from selected national immunization programs and other organizations were included if they were available online in English, Spanish, or French, and included information on the process for preparing multiple injections for a single child (reviewed references listed below). The search for national immunization guidelines was not comprehensive and is not representative of all national immunization programs. Several additional guidelines were reviewed but did not meet the above criteria (i.e. did not discuss process or had been accessed in other ways and are not available online).

Results

With the availability of vaccines that can be given as a third or fourth or fifth injection in a single vaccination visit, the process of preparing syringes for administration can become more complicated. Anecdotally, EPI staff from multiple countries report some countries are recommending a 'one at a time' process, where the first indicated vaccine is drawn up and administered to the infant, the second is drawn up and administered to the same infant, etc. This process raised concerns of an increased risk of injury and administration errors.

The Immunization Action Coalition (USA) recommends drawing up all of the vaccines indicated for one infant in a clean designated area, covering each clean needle with its cap, before administering all the indicated vaccines to the infant in quick succession. While recapping 'dirty' needles should be absolutely avoided to prevent needle stick injuries, 'clean' needles have no risk of blood-borne pathogen exposure for the health worker or the infant. The 2010 document *WHO best practices for injections and related procedures toolkit* recommends this practice, stating "If the dose cannot be administered immediately for any reason, cover the needle with the cap using a one-hand scoop technique". According to the CDC manual *Epidemiology and and Prevention of Vaccine Preventable Diseases*, also known as the CDC Pink Book, the practice of preparing all of the injections for an infant at one time differs from 'pre-loading' in that one dose of each indicated vaccine is prepared for a specific child present in the clinic and syringes are not used for storage, as the amount of time between drawing up and administration is still minimal (CDC discourages 'pre-loading')[1]. Similarly, the immunization guidelines from Public Health England and the Australian Government Department of Health recommend changing to a clean needle after drawing up the vaccine but before administration of the vaccine. Although not stated, this process also allows all indicated vaccines for a single child to be prepared, with the needles protected, and all of the vaccines to be administered in quick succession.

Overall, many guidelines reviewed did not have clear instructions for a preferred vaccine preparation process. We were unable to identify existing evidence to support one practice over another. An article by L.J. Tan and the SHAPE Vaccine Delivery Working Group similarly indicated that vaccine preparation and administration is an area that has not been critically evaluated and that guidance varies among programs [72].

References

American Academy of Pediatrics: http://redbook.solutions.aap.org/chapter.aspx?sectionid=56798089&bookid=886

Argentina EPI: http://www.msal.gov.ar/images/stories/bes/graficos/0000000451cnt-2013-06_recomendaciones-vacunacion-argentina-2012.pdf

Australian Government Department of Health:
http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/handbook10-2-2

Epidemiology and and Prevention of Vaccine Preventable Diseases (CDC Pink Book):
http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/D/vacc_admin.pdf

Immunization Action Coalition: http://www.immunize.org/guide/aov06_administer.pdf

Ministry of Health Kenya:
http://www.mchip.net/sites/default/files/mchipfiles/Immunization%20Manual%20for%20Medical%20and%20Nursing%20Students%20_final%20smaller.pdf

Public Health Agency of Canada: http://www.phac-aspc.gc.ca/publicat/cig-gci/p01-07-eng.php

Public Health England Green Book:
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/147915/Green-Book-Chapter-4.pdf

South Africa EPI: http://www.health-e.org.za/wp-content/uploads/2014/03/Vaccinators_Manual_Final.pdf

WHO: http://whqlibdoc.who.int/publications/2010/9789241599252_eng.pdf

Summary: WHO Vaccine Position Paper Review

Methods

All WHO vaccine positions papers available online at http://www.who.int/immunization/policy/position_papers/en/ as of 20 February 2015 were reviewed for content relating to co-administration of vaccines. In total, 22 position papers were reviewed. Information from the position papers was abstracted onto a standardized data collection form, including the date of position paper publication, the passages (verbatim) advising on co-administration, the page number of the Weekly Epidemiological Record where the information was found, and references cited in the position paper for the information (if any). Where a statement was made specifically as a WHO position on the vaccine, this was also noted. The information on co-administration was further coded into one of five categories:

1. Statements of multiple antigens existing as one combination injection;
2. Guidance that the antigen can be co-administered with other antigens (this may or may not have included advice on safety, reactogenicity and/or immunogenicity);
3. Guidance regarding possible reduced immunogenicity or increased adverse events with co-administration;
4. Guidance on spacing of two injections (e.g. 2.5 cm apart), location (e.g. thigh vs. deltoid), route of administration (e.g. intramuscular vs. subcutaneous) and/or preparation of injections (e.g. no mixing of vaccines in one syringe); or
5. Evidence gaps in the literature.

Results

Diphtheria

No guidance was presented.

***Haemophilus influenzae* type b (Hib)**

"Manufacturers indicate that Hib vaccine can be given safely and effectively at the same time as routine vaccines included in national immunization programmes. [Manufacturers' specifications] There is no conclusive evidence of differences in the immune response to monovalent or combined Hib conjugate vaccines. However, there is some evidence that Hib conjugate vaccine in combination with acellular pertussis (DTaP-Hib) induces a lower antibody response than Hib conjugate in combination with whole cell pertussis (DTwP-Hib) or separately administered DTaP and Hib conjugate vaccines." [83] "If Hib vaccine is given as a separate injection at the same time as other vaccines, it should be administered at a different site. It should not be mixed in the vial or syringe with any other vaccine unless it has been specifically manufactured and licensed for use in this way." [Manufacturers' specifications]

Hepatitis B

"The immune responses and safety of these combinations of Hepatitis B vaccines are comparable to those observed when the vaccines are administered separately."[84-86]

Pertussis

"None of the combination vaccines for pertussis (wP and aP) have produced adverse events that had not been observed with any of their separate components." [87] "However, there have been concerns that simultaneous exposure to multiple conjugate antigens could result either in enhanced or suppressed immune responses. A Cochrane review in 2009 found that use of the combined vaccines did not result in a significant increase in the incidence of serious adverse events but may cause more frequent minor reactions." [88]

PCV10 and PCV13

"The immunogenicity and reactogenicity of pneumococcal conjugate vaccines (PCV10 and PCV13) have been shown not to be significantly altered when PCVs are given concomitantly with monovalent or combination vaccines against diphtheria, tetanus, pertussis (acellular and whole-cell vaccines), hepatitis B, polio (inactivated and live oral vaccines), Hib, measles, mumps, rubella, varicella, meningococcus serogroup C (conjugate vaccine),

and rotavirus[this reference compares HIV infected to un-infected children]." [89] "When injected at different sites, PCVs can be administered concurrently with any other vaccines in infant immunization programmes."

PCV23

"Simultaneous administration of PCV23 does not increase adverse events or decrease the antibody response to either vaccine. The vaccine should not be mixed in the same syringe with other vaccines, for example with influenza vaccine, but may be administered at the same time by separate injection in the other arm."

IPV/OPV

"No clinically relevant interference has been reported when IPV is used in association with licensed diphtheria-tetanus-whole cell pertussis (DTwP)/ diphtheria–tetanus– acellular pertussis (DTaP), Hib, hepatitis B, pneumococcal polysaccharide conjugate or rotavirus vaccines." [90] "In developing country settings the simultaneous use of OPV and IPV has induced uniformly high antibody responses to all 3 poliovirus types, consistent with the use of multiple doses of poliovirus vaccines." [91] "IPV and OPV may be administered simultaneously and both can be given together with other vaccines used in national childhood immunization programmes. For rotavirus, interference [with OPV] has been noted after the first dose but not after completion of the full primary series." [92]

Tetanus

No information on tetanus vaccines regarding the antigen being co-administered with other antigens, possibility of reduced immunogenicity or increased adverse events with co-administration, or guidance on administration.

Conclusions

The WHO vaccine position papers mentioned the use of the following vaccines administered simultaneously with other vaccines in the routine schedule: Hib, wP/aP, PCV10/PCV13, PCV23, and IPV. There was no guidance on tetanus or diphtheria vaccines being co-administered alongside other antigens. No serious safety concerns were mentioned for any of the vaccines where guidance was available on simultaneous administration.

Table 5. Guidance from WHO Vaccine Position Papers by Vaccine Type

	WHO Guidance			
Vaccine (date of position paper)	**Antigen exists as a combination vaccine with other antigens**	**Antigen can be co-administered with other antigens (may or may not include advice on safety/reactogenicity/immunogenicity)**	**Possible reduced immunogenicity or increased adverse events with co-administration**	**Guidance on administration**
Haemophilus influenza type b (09/2013)	Hib vaccine is available in a variety of formulations: liquid Hib conjugate vaccine (monovalent), liquid Hib conjugate combined with diphtheria-tetanus-pertussis (DTP) and/ or hepatitis B; Hib conjugate in combination with meningococcal antigens; lyophilized Hib-conjugate with saline diluent (monovalent) and lyophilized Hib-conjugate for use with liquid DTP, or DTP in combination with other antigens – such as inactivated polio vaccine or hepatitis B vaccine.	Manufacturers indicate that Hib vaccine can be given safely and effectively at the same time as routine vaccines included in national immunization programmes. [Manufacturers' specifications]	There is no conclusive evidence of differences in the immune response to monovalent or combined Hib conjugate vaccines (ref). However, there is some evidence that Hib conjugate vaccine in combination with acellular pertussis (DTaP-Hib) induces a lower antibody response than Hib conjugate in combination with whole cell pertussis (DTwP-Hib) or separately administered DTaP and Hib conjugate vaccines. [83]	If Hib vaccine is given as a separate injection at the same time as other vaccines, it should be administered at a different site. It should not be mixed in the vial or syringe with any other vaccine unless it has been specifically manufactured and licensed for use in this way. [Manufacturers' specifications]
Hepatitis B (10/2009)	Hepatitis B vaccine is available as monovalent formulations or in fixed combination with other vaccines, including diphtheria–tetanus–pertussis (DTP), *Haemophilus influenzae* type b, hepatitis A and inactivated polio.	The immune responses and safety of these combinations of vaccines are comparable to those observed when the vaccines are administered separately.[84-86]		
Pertussis (wP & aP) (10/2010; revised guidance 07/2014)	Most wP vaccines are combined with diphtheria toxoid and tetanus toxoid. Some wP vaccines are also combined with other vaccines routinely administered during infancy, such as *Haemophilus influenzae* type b (Hib), hepatitis B (HBV) and inactivated poliovirus (IPV). (389) Although aP vaccines are usually administered in combination with diphtheria toxoid and tetanus toxoid, combinations containing aP vaccine may also include other	None of the combination vaccines have produced adverse events that had not been observed with any of their separate components. [87]	However, there have been concerns that simultaneous exposure to multiple conjugate antigens could result either in enhanced or suppressed immune responses. A Cochrane review in 2009 found that use of the combined vaccines did not result in a significant increase in the incidence of serious adverse events but may cause more frequent minor reactions.[88]	

	vaccines routinely administered during infancy, such as Hib, HBV, and IPV.			
Pneumococcus (PCV10 & PCV13) (04/2012)		The immunogenicity and reactogenicity of the involved vaccines have been shown not to be significantly altered when PCVs are given concomitantly with monovalent or combination vaccines against diphtheria, tetanus, pertussis (acellular and whole-cell vaccines), hepatitis B, polio (inactivated and live oral vaccines), Hib, measles, mumps, rubella, varicella, meningococcus serogroup C (conjugate vaccine), and rotavirus. [89] When injected at different sites, PCVs can be administered concurrently with any other vaccines in infant immunization programmes.		
Pneumococcus (PPV23) (10/2008)		Simultaneous administration does not increase adverse events or decrease the antibody response to either vaccine.		The vaccine should not be mixed in the same syringe with other vaccines, for example with influenza vaccine, but may be administered at the same time by separate injection in the other arm.
Polio (OPV & IPV) (02/2014)		OPV is usually administered concurrently with other vaccines including Bacillus Calmette-Guérin (BCG), diphtheria-pertussis- tetanus (DPT), hepatitis B, measles, and Hib, pneumococcal polysaccharide conjugate or rotavirus vaccines, because no interference with regard to effectiveness or adverse events has been observed with these vaccines.[79, 90, 92] No clinically relevant interference has been reported when IPV is used in association with licensed diphtheria-tetanus-whole cell pertussis	For rotavirus, interference has been noted after the first dose but not after completion of the full primary series.	

		(DTwP)/ diphtheria–tetanus– acellular pertussis (DTaP), Hib, hepatitis B, pneumococcal polysaccharide conjugate or rotavirus vaccines. [90] In developing country settings the simultaneous use of OPV and IPV has induced uniformly high antibody responses to all 3 poliovirus types, consistent with the use of multiple doses of poliovirus vaccines. [91] IPV and OPV may be administered simultaneously and both can be given together with other vaccines used in national childhood immunization programmes.		
Tetanus (05/2006)	Tetanus toxoid vaccines are available as single toxoid (TT), combined with diphtheria toxoid (DT) or low-dose diphtheria toxoid (dT) and in combination with diphtheria and pertussis vaccines (DTwP, DTaP, dTaP or dTaP)… Several new combinations containing DTP/DTaP have been marketed, including vaccines against hepatitis B, Haemophilus influenzae type b and poliomyelitis.			

Summary: Expert Comment and Additional Information

Expert Comment

We asked experts in immunology to provide comments on evidence relevant to topics 1, 3, and 4.

1. Non-inferiority (immunogenicity and adverse events) of giving two or more injections in the same limb compared to administration in different limbs.
3. Basis for the recommendation of giving two injections 2.5 cm (1 inch) apart.
4. Recommendation of not using the deltoid for intramuscular injections in infants.

None could refer us to any literature directly addressing topics 1, 3, and 4.

Global and Regional Status of the Number of Injectable Vaccinations

Source: WHO/UNICEF joint reporting form process: national immunization schedules, 2014.
Available at: http://apps.who.int/immunization_monitoring/globalsummary/schedules

Table 4. Number of injectable vaccinations recommended in a single visit for infants and children 0-2 years of age as of 2015

	Global	AFR	AMR	EMR	EUR	SEAR	WPR
# of countries with data	194	47	35	21	53	11	27
# with 2 injectable vaccine visits	159	35	27	20	42	8	26
# with 3 injectable vaccine visits	47	1	13	7	17	1	9
# with 4 injectable vaccine visits	16	0	6	3	4	0	3
# with 5 injectable vaccine visits	5	0	0	0	5	0	0
% with 2 injectable vaccine visits	82%	74%	77%	95%	79%	73%	96%
% with 3 injectable vaccine visits	24%	2%	37%	33%	32%	9%	33%
% with 4 injectable vaccine visits	8%	0%	17%	14%	8%	0%	11%
% with 5 injectable vaccine visits	3%	0%	0%	0%	9%	0%	0%
Average proportion of total visits with:							
1 injectable vaccine	56%	58%	57%	42%	55%	71%	58%
2 injectable vaccines	35%	42%	28%	47%	30%	27%	32%
3 injectable vaccines	6%	1%	11%	7%	9%	2%	8%
4 injectable vaccines	2%	0%	4%	3%	2%	0%	2%
5 injectable vaccines	1%	0%	0%	0%	2%	0%	0%

Median # of visits	6	5	7	6	7	6	6
# with IPV already*	69	1	6	11	41	0	10
% with IPV already*	36%	2%	17%	52%	77%	0%	37%

Countries Planning to Introduce IPV as a 3rd Injection in a Single Visit

Table 5. Countries planning to introduce IPV as a 3rd injection in a single visit by April 2016 by WHO region*

IPV-Vaccine is a third injection	Number of Countries
Don't know	**72**
AFR Central	8
AFR East and South	1
AFR West	16
Americas	29
Eastern Mediterranean	2
Europe	12
South East Asia	2
Western Pacific	2
No	**28**
AFR East and South	4
AFR West	1
Eastern Mediterranean	6
South East Asia	9
Western Pacific	8
Yes	**26**
AFR Central	2
AFR East and South	14
Eastern Mediterranean	4
Western Pacific	6
Total	**126**

*Updated March 3rd, 2015.

Year of Introduction and Number of Immunogenic Proteins and Polysaccharides Contained in Selected Vaccines

Table 6. Reproduction of Table 76-3 from Vaccines (6th Edition), p. 1471 [79]

Table 76-3 Year of Introduction and Number of Immunogenic Proteins and Polysaccharides Contained in Selected Vaccines		
Vaccine	**Year of Introduction**	**No. of proteins or polysaccharides or both**
Smallpox*	1796	196
Rabies	1885	5
Diphtheria†	1923	1
Pertussis (whole-cell)*	1926	~3,000
Tetanus†	1927	1
Yellow fever	1936	11
Influenza	1945	10
Polio (inactivated) †	1955	15
Polio (live attenuated)*	1961	15
Measles†	1963	10
Mumps†	1967	9
Rubella†	1969	5
Hepatitis B†	1981	1
H. influenzae type b (conjugate) †	1990	2
Pertussis (acellular)	1991	2-5
Hepatitis A†	1995	4
Varicella†	1995	69
Pneumococcus (conjugate)†	2000	14
Meningococcus (conjugate)†	2005	5
Rotavirus†	2006	11-16
Human papillomavirus†	2006	2-4

*Formerly in the US routine child and adolescent immunization schedule

†Currently in the US routine child and adolescent immunization schedule

Key Conclusions

Key Conclusions and Recommendations:

- IPV (non-adjuvanted) can be safely and effectively given intramuscularly (IM) or subcutaneously (SC). However, the IM route is generally less reactogenic for inactivated vaccines. When IPV is administered as part of a combination vaccine, the route of administration should also reflect the optimal route for the other antigens in the combination vaccine.
- Intramuscular injection sites should be chosen to minimize the risk of nerve and muscle injury from the act of inserting a needle into the muscle and to maximize the probability of an adequate immune response. Systematic comparisons of the risks and benefits of different possible intramuscular injection sites for infants are lacking, but the vastus lateralis (thigh) muscle is a viable site with the ventrogluteal (hip) muscle as an acceptable alternative. The deltoid (upper arm) muscle is another viable site for children, with 12 through 18 months being common ages for the initiation of the use of this site. However, the use of the deltoid may need to be delayed if the muscle is atrophied. The dorsagluteal site (buttock) is not recommended due to the high risk of injury.
- The schedule used for vaccinating children should maximize the likelihood that the children will be fully protected against vaccine preventable diseases while minimizing the risks of vaccine adverse events. For infants, administering the DTP-Hepatitis B-Hib vaccine, IPV, and a PCV at the same visit, all intramuscularly, is a viable option for achieving these goals. Systematic comparisons of the risks and benefits of the various possible sites for administering infants DTP-Hepatitis B-Hib vaccine, IPV, and a PCV at the same visit are lacking, but injecting DTP-Hepatitis B-Hib vaccine in one thigh and IPV and PCV in another thigh can be done safely and effectively.
- If two vaccines are injected into the same muscle, they should ideally be spaced far enough apart to allow any localized adverse events they cause to be distinguished. Systematic studies of the best distance for separating vaccine injections are lacking, although a 2.5 cm distance between injections to the vastus lateralis (thigh) or deltoid is a viable option.
- If multiple injectable vaccines are administered in a single visit, care must be taken in the drawing up and preparation of each vaccine. Drawing up all of the vaccines needed for an infant in a clean designated area, covering each clean needle with its cap using a one-hand scoop technique, and then administering of the indicated vaccines to the infant in quick succession is a viable approach. Needles should not be recapped after being used for an injection.
- Countries introducing new vaccines which will increase the number of injections per immunization visit should be strongly encouraged to:
    - Ensure healthcare providers receive information that the safety and biologic effects of providing all recommended vaccines in single visits are generally similar to those of providing them in separate visits, as well as training on communication techniques with parents who may have concerns about the child receiving multiple vaccine injections in a single visit.
    - Develop national vaccination schedules that include multiple vaccine injections in a single visit unless specific evidence exists that doing so will have negative repercussions which outweigh the benefits of administering multiple vaccines in a single visit. Administering multiple injectable vaccines in a single visit may lower costs to the health care system and vaccine recipients and reduce drop-out rates.
    - Monitor the acceptance and effects of simultaneous administration of injectable vaccines per their national vaccination schedule recommendations as a means to identify if any short or long-term problems result from recommending the simultaneous administration of injectable vaccines.
- Due to the variability of the effects of the different combinations of vaccines than can be co-administered in one visit, vaccination schedules should adapt to new data on the adverse events and immunogenicity of specific vaccine combinations as they become available.

Annex

Excerpts from Published Guidance and Recommendations

Table 4. Recommendations by Committee

Committee	Country	Guidance/Recommendations
General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP)[52]	USA	Takes a flexible approach to vaccine administration for multiple injections Simultaneous Administration, p.6 "Simultaneous administration of vaccines is defined as administering more than one vaccine on the same clinic day, at different anatomic sites, and not combined in the same syringe. Experimental evidence and extensive clinical experience provide the scientific basis for administering vaccines simultaneously." "With some exceptions, simultaneously administering the most widely used live and inactivated vaccines has produced seroconversion rates and rates for adverse reactions similar to those observed when the vaccines are administered separately [49, 93-95]. Routine administration of all age-appropriate doses of vaccines simultaneously is recommended for children for whom no specific contraindications exist at the time of the visit. MMR and varicella vaccine can be administered simultaneously." "Depending on which vaccines are administered during the first year of life, a child might receive up to nine injections at the 12- through 15-month visit (MMR, varicella, Hib, pneumococcal conjugate vaccine [PCV], pediatric diphtheria and tetanus toxoids and acellular pertussis [DTaP], inactivated poliovirus [IPV], hepatitis A, hepatitis B, and influenza vaccines). Although there is no exact limit on the number of injections, with a little flexibility, a provider can ensure that the primary series doses are given without administering too many injections at each visit. To reduce the number of injections at the 12- through 15-month visit, the hepatitis B series and 3 doses of IPV (*20*) can be administered before the child's first birthday." "There are many other examples of ways the vaccination schedule provides flexibility." "The minimum age for administration of combination vaccines is the oldest minimum age for any of the individual components; the minimum interval between doses is equal to the greatest minimum interval of any of the individual components. With use of the combination Hib-hepatitis B vaccine, the minimum age of administration of the final dose is 12 months because of the minimum age requirement for the last dose of the Hib series (*26*)." Non-simultaneous Administration, p. 8 "There is no evidence that inactivated vaccines interfere with the immune response to other inactivated vaccines or to live vaccines. Any inactivated vaccine can be administered either simultaneously or at any time before or after a different inactivated vaccine or live vaccine (Table 3). Limited data are available regarding interference between live vaccines used in the United States. The immune response to one live-virus vaccine might be impaired if administered within 28 days (i.e., 4 weeks) of another live-virus vaccine (*52,*

		53).” Route of Administration, p. 14 Intramuscular Injections ***Infants (Aged <12 months)*** For the majority of infants, the anterolateral aspect of the thigh is the recommended site for injection because it provides a large muscle mass (Figure 2). In certain circumstances (e.g., physical obstruction to other sites and no reasonable indication to defer doses), the gluteal muscle can be used. If the gluteal muscle must be used, care should be taken to define the anatomic landmarks.§§ Injection technique is the most important parameter to ensure efficient intramuscular vaccine delivery. If the subcutaneous and muscle tissue are bunched to minimize the chance of striking bone (*95*), a 1-inch needle is required to ensure intramuscular administration in infants aged ≥1 month. For the majority of infants, a 1-inch, 22- to 25-gauge needle is sufficient to penetrate the thigh muscle. For neonates (first 28 days of life) and preterm infants, a ⅝-inch needle usually is adequate if the skin is stretched flat between the thumb and forefinger and the needle is inserted at a 90-degree angle to the skin (*97*). ***Toddlers (Aged 12 Months- 2 Years)*** For toddlers, the anterolateral thigh muscle is preferred, and if used, the needle should be at least 1 inch long. The deltoid muscle can be used if the muscle mass is adequate. A ⅝-inch needle is adequate only for the deltoid muscle and only if the skin is stretched flat between thumb and forefinger and the needle is inserted at a 90-degree angle to the skin. ***Children (Aged 3-18 Years)*** The deltoid muscle is preferred for children aged 3--18 years (Figure 3); the needle size for deltoid site injections can range from 22 to 25 gauge and from ⅝ to 1 inch on the basis of technique. Knowledge of body mass can be useful for estimating the appropriate needle length (*99*); however, neither a physical examination nor measurement of body mass is necessary to administer vaccines. Most children in this age range require a ⅝- or 1-inch needle (or intermediate size, if available). **Multiple Injections** If multiple vaccines are administered at a single visit, administer each preparation at a different anatomic site. For infants and younger children, if more than two vaccines are injected in a single limb, the thigh is the preferred site because of the greater muscle mass; the injections should be sufficiently separated (i.e., ≥1 inch if possible) so that any local reactions can be differentiated (*92,100*). For older children and adults, the deltoid muscle can be used for more than one intramuscular injection. If a vaccine and an immune globulin preparation are administered simultaneously (e.g., Td/Tdap and tetanus immune globulin [TIG], hepatitis B and hepatitis B immunoglobulin [HBIG]), separate anatomic sites (i.e., different limbs) should be used for each injection. The location of all injection sites should be documented in the patient's medical record. Health-care practices should consider using a vaccination site map so that all persons administering vaccines routinely use a particular anatomic site for each different vaccine.
American		“Simultaneous administration of most vaccines is safe, effective and

Academy of Pediatrics – Report of the Committee on Infectious Diseases (Red Book): Simultaneous Administration of Multiple Vaccines 2012 [96]		recommended. Infants and children have sufficient immunologic capacity to respond to multiple vaccines. No contraindications to the simultaneous administration of multiple vaccines routinely recommended for infants and children are known. Immune response to one vaccine generally does not interfere with responses to other vaccines. Simultaneous administration of IPV, MMR, varicella, or DTaP vaccines results in rates of seroconversion and of adverse effects similar to those observed when the vaccines are administered at separate visits. MMRV is associated with a higher rate of fever and febrile seizures after the recommended first dose than MMR and varicella administered separately at the same visit. Because simultaneous administration of routinely recommended vaccines is not known to affect the effectiveness or safety of any of the recommended childhood vaccines, simultaneous administration of all vaccines that are appropriate for the age and immunization status of the recipient is recommended. [52] When vaccines are administered simultaneously, separate syringes and separate sites should be used, and injections into the same extremity should be separated by at least 1 inch so that any local reactions can be differentiated. Simultaneous administration of multiple vaccines can increase immunization rates significantly. Some vaccines administered simultaneously may be more reactogenic than others (see disease-specific chapters). Individual vaccines should never be mixed in the same syringe unless they are specifically licensed and labeled for administration in one syringe. If an inactivated vaccine and an immune globulin product are indicated concurrently (eg, hepatitis B vaccine and HBIG, rabies vaccine and RIG), they should be administered at separate anatomic sites."
Public Health Agency of Canada, 2013 [50]	Canada	*Subcutaneous (SC) injections* For infants younger than 12 months of age, the usual site for SC administration of vaccine is the subcutaneous tissue of the anterolateral thigh; if necessary, the upper triceps area of the arm may be used. SC injections for vaccine recipients 12 months of age and older are usually given into the subcutaneous tissue of the upper triceps area of the arm. SC injections should be administered at a 45° angle. *Intramuscular (IM) injections* IM injections of vaccine are administered at a 90° angle into the vastus lateralis muscle (anterolateral thigh) in infants less than 12 months of age and into the deltoid muscle of persons 12 months of age and older (unless the muscle mass is not adequate, in which case the anterolateral thigh can be used). For the injection of diphtheria, tetanus, acellular pertussis (DTaP) vaccine in children 12 to 35 months of age, the deltoid muscle or anterolateral thigh can be used. A large retrospective cohort study of children 12 to 35 months of age demonstrated a lower risk of medically- attended local reactions when DTaP vaccine was given into the thigh compared to vaccination into the arm. Appropriate site selection is important to avoid inadvertent injection into a blood vessel or injury to a nerve. Vaccines containing adjuvants must be injected intramuscularly. If a vaccines containing an adjuvant is inadvertently injected subcutaneously or intradermally, increased inflammation, induration or granuloma formation may occur. Refer to Immunization of Persons with Chronic Diseases in Part 3 for additional information about IM administration

		of vaccines to people with bleeding disorders. Active immunizing agents should not be administered into the buttock (gluteal muscle). Immunogenicity is lower to hepatitis B and rabies vaccines if given in the buttock, probably because of injection into adipose tissue where the vaccine is not well absorbed. The buttock is an acceptable site for administration of immune globulin when large volumes are administered, and activation of the immune system is not required, but appropriate site selection of the gluteal muscle is necessary to avoid injury to the sciatic nerve. *Multiple injections* All opportunities to immunize should be used and giving multiple vaccines at the same clinic visit is encouraged. Giving multiple injections at one visit helps to ensure that individuals are up to date with the vaccines required for their age and risk factors. Generally, infants and children have similar immune responses whether vaccines are given at the same time or at different visits. Although children are now receiving more vaccines, they are exposed to fewer antigenic proteins in today's vaccines than in the vaccines used in the past, because of changes in the vaccine products. Practice considerations for multiple injections include the following: - Label syringes to identify which vaccine each syringe contains. - Record the site of administration of each vaccine, so that if an injection site reaction occurs, the associated vaccine can be identified. - Use separate limbs if two IM injections are required. If more than two injections in the same limb are required, administer the two injections into the same muscle, separated by at least 2.5 cm (1 inch). In cases where there is insufficient deltoid muscle mass, the anterolateral thigh can be used. - Administer vaccines that are known to cause more stinging or pain after other vaccines (e.g., Prevnar®13; M-M-R®II, human papillomavirus vaccines [HPV]). - If a vaccine and an immune globulin preparation are administered simultaneously (e.g., tetanus toxoid-containing vaccine and tetanus immune globulin), use separate anatomic sites (different limbs) for each injection.
The Australian Immunisation Handbook, 2013 [51]	Australia	**Vaccines administered IM or SC** Influenza vaccine† Measles-mumps- rubella vaccine (MMR) (Priorix only) Measles-mumps-rubella-varicella vaccine (MMRV) (Priorix-tetra only) 23-valent pneumococcal polysaccharide vaccine (23vPPV)† Rabies vaccine (HDCV) Yellow fever vaccine * IPV-containing combination vaccines are administered by IM injection; IPV (IPOL) is administered by SC injection. ***2.2.9 Administering multiple vaccine injections at the same visit***

		When sequentially administering multiple vaccines to children, give the most painful vaccine last (e.g. pneumococcal conjugate vaccine). Evidence suggests that this may decrease the overall pain response. The location of each separate injection given should be recorded, so that if a local adverse event occurs, the implicated vaccine(s) can be identified. **Infants <12 months of age** The vastus lateralis muscle in the anterolateral thigh is the recommended site for IM vaccination in infants <12 months of age, due to its larger muscle size. The suitable sites for this age group are the anterolateral thighs (preferred) and the ventrogluteal areas. For the routine schedule where only two vaccines are required, one can be given in each thigh. When three or four injectable vaccines are to be given at the same visit, the options are: - two injections in the same anterolateral thigh, separated by at least 2.5 cm (see Figure 2.2.10, injection numbers 1 and 2); further IM vaccines can be given in this way in the other thigh (injection number 3), or - one injection into each anterolateral thigh and one injection into each ventrogluteal area (only one injection should be given into each ventrogluteal area).
Public Health England – Immunisation Against Infectious Disease, 2013 [97]	England	The anterolateral aspect of the thigh is the preferred site for infants under one year old, because it provides a large muscle mass into which vaccines can be safely injected. Where two or more injections need to be administered at the same time, they should be given at separate sites, preferably in a different limb. If more than one injection is to be given in the same limb, they should be administered at least 2.5cm apart (American Academy of Pediatrics, 2003). The site at which each injection is given should be noted in the individual's records.
General Immunization Practices in *Vaccines* 6th Ed. [98]	N/A	"Unless specifically licensed for injection in the same syringe, different vaccines administered simultaneously should be injected separately and at different anatomic sites. If both upper and lower limbs must be used for simultaneous administration of different vaccines, the anterolateral thigh is often chosen for intramuscular injections and the triceps region for subcutaneous injections. If more than one injection must be administered in a single limb of an infant or young child, the thigh usually is preferred because of its large muscle mass. The distance separating two injections in the same limb should be sufficient (eg, 1 to 2 inches) to minimize the chance of overlapping local reactions. [5, 12, 13] In general, different vaccines, including live virus products, can be administered simultaneously without reducing their safety and effectiveness [62] (Table 8-4). Studies of cortisol concentration and behavioral responses to vaccination indicate that responses are similar in infants who receive two injections during one visit and infants who receive a single injection, suggesting that a second injection does not increase stress. [63, 64] Increased severity or incidence of adverse reactions has not been observed after simultaneous administration of the most widely used vaccines. [5] Similarly, simultaneous administration of vaccines generally does not cause immunologic interference except possibly between pneumococcal conjugate

		vaccine and Menactra brand meningococcal conjugate vaccine." [62, 64]
American Academy of Pediatrics – Report of the Committee on Infectious Diseases (Red Book): Site and Route of Immunization (Active and Passive) (2012) [99]		"For IM injections, the choice of site is based on the volume of the injected material and the size of the muscle, and the needle should be directed at a 90° angle. In children younger than 1 year of age (ie, infants), the anterolateral aspect of the thigh provides the largest muscle and is the preferred site. In older children, the deltoid muscle usually is large enough for IM injection." "When multiple vaccines are administered, separate sites ordinarily should be used if possible, especially if one of the vaccines contains DTaP. When necessary, 2 or more vaccines can be given in the same limb at a single visit. The anterolateral aspect of the thigh is the preferred site for multiple simultaneous IM injections because of its greater muscle mass. The distance separating the injections is arbitrary but should be at least 1 inch, if possible, so that local reactions are unlikely to overlap."
Centers for Disease Control and Prevention – Epidemiology and Prevention of Vaccine-Preventable Diseases [100]	USA	General recommendations on Immunization Chapter: "Simultaneous administration (that is, administration on the same day) of the most widely used live and inactivated vaccines does not result in decreased antibody responses or increased rates of adverse reaction. Simultaneous administration of all vaccines for which a child is eligible is very important in childhood vaccination programs because it increases the probability that a child will be fully immunized at the appropriate age. A study during a measles outbreak in the early 1990s showed that about one-third of measles cases in unvaccinated but vaccine-eligible preschool children could have been prevented if MMR had been administered at the same visit when another vaccine was given. All indicated vaccines should be administered at the same visit. There is one exception to this rule. In children with functional or anatomic asplenia pneumococcal conjugate vaccine (PCV) and Menactra brand meningococcal conjugate vaccine should not be administered at the same visit, and should be separated by at least 4 weeks. This is because children with functional or anatomic asplenia are at very high risk of pneumococcal invasive disease and Menactra is thought to interfere with the antibody response to PCV. Individual vaccines should not be mixed in the same syringe unless they are licensed for mixing by the Food and Drug Administration. Only the sanofi-pasteur DTaP-IPV/ Hib (Pentacel) vaccine is licensed for mixing in the same syringe. See Appendix D for additional guidelines for vaccine administration. Combination vaccines are generally preferred over simultaneous administration of single component vaccines. Considerations should include an assessment of the number of injections, vaccine availability, likelihood of improved coverage, likelihood of patient return, and storage and costs. Considerations should also include patient choice and the potential for adverse events. For the first dose of vaccine to prevent measles, mumps, rubella and varicella, unless the parent or caregiver expresses a preference for MMRV vaccine, separate MMR and Varicella vaccines should be administered for children 12 through 47 months of age." Appendix: Vaccine Administration Guidelines: "If multiple vaccines are

		administered at a single visit, administration of each preparation at a different anatomic site is desirable. For infants and younger children, if more than two vaccines are injected in a single limb, the thigh is the preferred site because of the greater muscle mass. For older children and adults, the deltoid muscle can be used for more than one intramuscular injection. The injection sites should be separated by 1 inch or more, if possible, so that any local reactions can be differentiated. Vaccines that are the most reactive (e.g., tetanus-containing and PCV) should be administered in different limbs if possible. Use of combination vaccines can reduce the number of injections.”

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Report to SAGE on reducing pain and distress at the time of vaccination

24 March 2015

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Executive Summary

Although pain that develops in the hours to days after an injectable vaccine is relatively well-studied, significantly fewer resources and recommendations have been developed to prevent or mitigate pain or distress at the time of vaccination. Injection pain has been shown to cause distress for children and adults and onlookers, including health personnel giving the injection.

Fear of an injection as a result of poorly managed procedure pain can lead to vaccine hesitancy. A delay or avoidance of future vaccinations is associated with lower vaccination coverage rates which puts the individual and the public's health at risk due to the potential for outbreaks of vaccine-preventable disease. To address this iatrogenic harm at the vaccination event in the vaccination process, the World Health Organization's (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) identified the prevention and mitigation of pain and distress at the time of vaccination as one strategy to address vaccine hesitancy.

An evidence based approach was used to adapt existing evidence reviews and to develop recommendations relevant for low and middle income country settings. Some of the strategies to mitigate pain and distress at the time of vaccination will be familiar to practitioners but the evidence base and the imperative to act to prevent pain and distress are new. The evidence for each of the recommendations pragmatically incorporated low and middle income countries (LMIC) patient values and preferences, estimates on impact on equity, and the feasibility, acceptability and costs of the intervention.

The recommendations were developed for consideration at the SAGE April 2015 meeting. They relate to interventions to reduce pain and distress at the time of vaccination, as well as on strategies for implementation. Interventions that were impractical (e.g. such as those requiring substantial resources to implement), ineffective, potentially harmful, and/or without evidence of effectiveness, were not recommended.

Research and implementation gaps relevant for global settings were identified.

The following examples serve to highlight a few of the evidence-based recommendations. For a more complete list of recommendations please see the report:

- Do NOT aspirate when giving vaccines to all ages (strong recommendation)
- Administer vaccines from the least to the most painful vaccine for all ages (strong recommendation)
- Breastfeed at time of vaccinations for infants (conditional recommendation: for women who are breastfeeding and for whom breastfeeding during the vaccination session is culturally acceptable in the vaccination setting)
- Use neutral words at the time of vaccination; avoid language that increases anxiety (strong recommendation) for all ages

Introduction

Background

The relief of pain or distress during health-related procedures is a basic human right.[1] In recent years, there has been an increasing emphasis on measuring and tracking adverse effects from vaccinations. Although pain that develops in the hours to days after an injectable vaccine is relatively well-studied, significantly fewer resources have been devoted to understanding and mitigating pain at the time of the vaccination event. The Child-Friendly-Healthcare Initiative, developed by Child Advocacy International in the UK and endorsed by WHO and UNICEF, has recommended the development of standards and guidelines for the assessment of pain and discomfort, and that invasive procedures must be accompanied by adequate analgesia.[2] Pain at the time of vaccine injection has been defined as an Adverse Event Following Immunization (AEFI) from global research collaborations such as the Brighton Collaboration, and in need of assessment and management from the global immunization community.[3,4] Furthermore, at the October 2014 SAGE meeting, the Working Group on Vaccine Hesitancy identified the mitigation of pain at the time of vaccination as one strategy to address vaccine hesitancy.[5] Vaccine injection pain and/or fear of needles are documented concerns for vaccine recipients, caregivers, and those giving the injection, and are documented to lead to hesitancy.[6] However, no evidence on strategies for the mitigation of pain at the time of vaccination pain has been retrieved in the systematic reviews of strategies to address hesitancy.[7,8] To date, WHO has not provided any specific guidance document about how to mitigate pain at the time of vaccination.

Burden of pain and distress during vaccination

Vaccine injections are a common source of iatrogenic pain in childhood.[9] Fear of needles is extremely common. In a survey on the prevalence of needle fears in children, 63% of children and 24% of adults reported they were at least a little afraid of needles. Approximately 40% of parents are concerned with pain during childhood vaccinations, 85% believe that doctors and nurses have a responsibility to make vaccinations less painful, and 95% wish to learn how to reduce pain in their children.[6,10] Furthermore, the most common concern for parents of children receiving multiple injections in one visit was pain.[10] A recent study from South Africa examining attitudes toward the use of multiple injections found them to be acceptable by health care workers and by parents but called for strategies to mitigate pain.[11]

Research from high income countries has shown that pain at the time of vaccination has effects on the individuals involved in the administration and receipt of vaccines, and society more broadly.[3] The person receiving the vaccine is subjected to the possibility of pain, and the experience can be negative not only for the vaccine recipient but also for health care providers and other onlookers such as parents, guardians and siblings.[3] Fear and worry about the pain may intensify the experience of pain.[12 13 14 15] Longer term, repeated painful and negative experiences with vaccinations can lead to avoidance of future vaccination[3] putting the individual and the public's health at risk. Furthermore, people distressed by receipt of vaccines may be more likely to avoid needle-procedures in other areas of health care, leading to poorer health outcomes.[3] Interventions to mitigate pain and fear during vaccination and prevent the potential negative long-term consequences but have been underutilized.[3]

Measuring pain

There are four general ways to assess pain: self-report measures, behavioural measures, observer reports, and physiological measures. Because pain is subjective, self-report measures are generally assigned the most weight. Different self-report measures are recommended at different ages. For example, children 3-4 years old may use the *Pieces of Hurt Tool*, pointing to the number of circles corresponding to their level of pain. Children 4-12 years may use the *Faces Pain Scale-Revised* which has them select the facial drawing corresponding to the level of pain expression they are feeling.[16] Children 8 years or more and adults can use the *Numerical Rating Scale*.[17] Behavioural measures can be used to provide information about pain. Validated tools such as the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) assess a broad band of behaviours such as crying, facial expression, leg positioning, and others, for a total score between 4-13.[18] Similar tools include the Face, Legs, Activity, Cry, Consolability Observational Tool (FLACC)[19] and the Modified Behavioural Pain Scale (MBPS).[20] Behavioural measures also include tools that rely on fine-grained coding of facial expressions, such as the Neonatal Facial Coding System (NFCS), Child Facial Coding System (CFCS), and Facial Action Coding System (FACS).[19] Observer reports typically involve having observers (e.g., parents, health professionals) use some of the same tools used by children to provide self-reports (e.g. faces scales).

Physiological measures examine changes in body processes such as heart rate, vagal tone, respiratory rate, oxygen saturation, palmar sweating, skin blood flow and intracranial pressure. Physiological measures are not specific to pain and have been shown to habituate to pain and are therefore not very valuable as an outcome measure of pain.

There is no simple relationship between the amount of tissue damage and pain. Anticipatory anxiety (or fear) can impact on the pain experience. As such, it is important to mitigate not only pain but fear as well. Since proxy reports and observational methods typically cannot distinguish between fear and pain, the term used to describe what is being measured by them is distress. While this report focuses on pain as the over-arching concept, the words fear and distress are also used throughout to describe the evidence base for included interventions, as relevant.

Evidence based clinical practice guidelines

In 2008, the *Help ELiminate Pain in KIDS Team (HELPinKIDS)* was assembled in Canada. This independent, multi-disciplinary team was tasked with addressing the gap between numerous evidence-based treatments to mitigate vaccination pain and the fact that many individuals do not benefit from their use.[3] The HELPinKIDS team synthesized the research evidence and published the first Clinical Practice Guideline (CPG) on this topic in 2010.[9] Due to numerous new studies as well as demand from stakeholders to address new interventions, the HELPinKIDS CPG was updated in 2015.[3] The expanded and updated *HELPinKIDS 2.0 Clinical Practice Guideline for Reducing Pain and Fear from Vaccine Injections in Children and Adults* formed the basis for the recommended interventions.

Technical consultation group members

In order to determine if and how the Canadian clinical practice guidelines could be adapted to WHO recommendations, a technical consultation was held on 16-17 February 2015 at WHO HQ in Geneva. The group of experts invited for the consultation and contributing to this report was composed of:

1. K. O. Antwi-Agyei, Immediate Past National Programme Manager, Expanded Programme on Immunisation, Disease Control and Prevention Department, Ghana Health Service, Accra,

Ghana (expert consultant, also member of the WHO Immunization Practices Advisory Committee)

2. Christine Chambers, Professor, Departments of Pediatrics/Psychology and Neuroscience, , Dalhousie University, and Centre for Pediatric Pain Research, IWK Health Centre, Halifax, Nova Scotia, Canada (co-author of HELPinKIDS 2.0 CPG)
3. Liesbet Goubert, Professor, Department of Experimental-Clinical and Health Psychology, Ghent University, Belgium (expert consultant)
4. Darunee Jongudomkarn, Associate Professor, Faculty of Nursing, Khon Kaen University, Thailand (expert consultant)
5. Noni MacDonald, Professor, Department of Paediatrics, Dalhousie University, IWK Health Centre and Canadian Center for Vaccinology, Halifax, Nova Scotia, Canada (co-author of HELPinKIDS 2.0 CPG)
6. Anna Taddio, Professor, Leslie Dan Faculty of Pharmacy, University of Toronto, and Senior Associate Scientist, The Hospital for Sick Children, Toronto, Ontario, Canada (Lead author of HELPinKIDS 2.0 CPG)
7. Nikki Turner, Associate Professor and Director, Immunisation Advisory Centre, University of Auckland, New Zealand (SAGE Focal Point) – Participated in the consultation via phone connection

Lidia Oliveira, Senior Medical Manager - Europe – Vaccines, Pfizer also contributed on the phone to the discussions on the industry perspective for which she served as an industry representative.

The technical consultation and/or report writing was supported by the WHO's SAGE Secretariat (Philippe Duclos, Neeta Gurnani, Kevin Pottie, Melanie Schuster, Winnie Siu). Philippe Duclos, Neeta Gurnani, and Winnie Siu attended the face-to-face technical consultation.

It was agreed that the focus of the consultation would be on mitigation of pain, distress and fear during the vaccination event; i.e., acute pain (not delayed pain, which occurs in the hours to days thereafter) and that specific interventions for individuals with high levels of needle fear would not be included, but with the understanding that reducing pain will likely also prevent the development of high levels of needle fear in the future.

The group would like to acknowledge the work of Meghan McMurtry, Assistant Professor, Guelph University) who allowed the timely updating of the analysis of HELPinKIDS 2.0 CPG from which this report benefited.

Declaration of Interests

All invited experts except Lidia Oliveira, the industry representative, completed a declaration of interests. Two experts reported relevant interests. All interests were assessed not to constitute a conflict of interest in regard to contributing to the technical consultation. It was concluded that all members could take part in full in all of the discussions. The industry representative did not participate in discussions other than that of the industry perspective and was not involved in decision-making. The complete Declaration of Interests can be found in Appendix 1.

Methods

Overview

We used the *GRADE_DECIDE* process to adapt existing evidence for low and middle income country (LMIC) and differing geographical and cultural settings. This method included identifying potential interventions relevant and culturally acceptable for LMIC, identifying systematic review evidence to determine the trade-offs between benefits and harms, and then using literature and expert advice to explicitly document estimates for patient values and preferences, equity impacts, feasibility, acceptability, and costs. This process provided the evidence to determine interventions which were recommended and interventions which were not recommended.

Systematic review evidence

The 2015 HELPinKIDS 2.0 Clinical Practice Guidelines project selected and reviewed 55 different interventions designed to mitigate pain and fear during immunization injections.[i] In total, 136 articles were reviewed which had a predominance from high-income countries and the region of the Americas but included representation from every WHO region (see Figure 1).

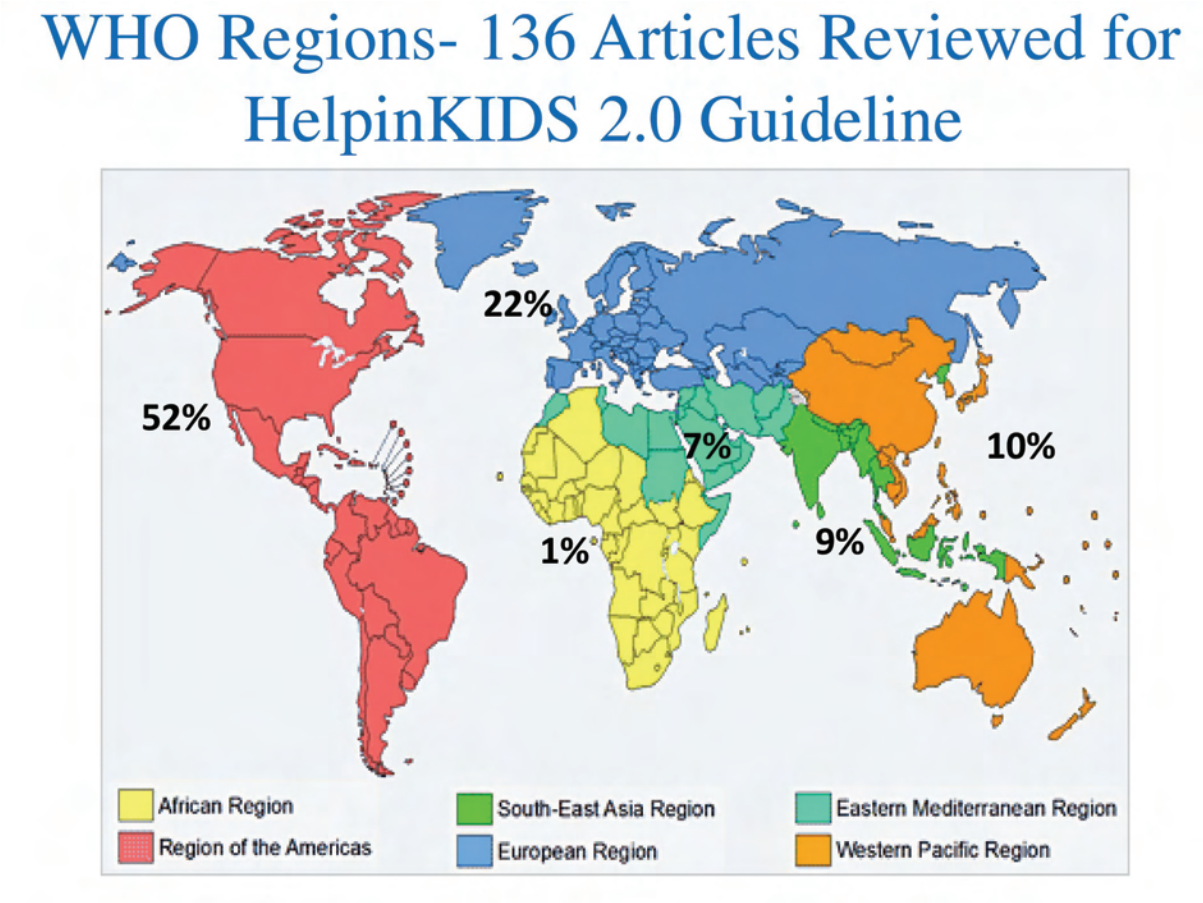

Figure 1: Percentage of reviewed articles by WHO region

The evidence-based GRADE (Grading of Assessments, Recommendations, Development and Evaluation)[21] and Cochrane methodologies provided the general framework for the systematic

[i] As a result of the interaction in the context of the SAGE review, HELPinKIDS 2.0 was adjusted and the number of interventions reflected in this report departs from the initial set of 52 interventions listed in the project when the technical consultation took place. This report is consistent with the revised version of HELPinKIDS 2.0 accessible on the SAGE website.

reviews that were used to appraise and synthesize the research evidence and formulate the recommendations. The literature review considered randomized controlled trials and quasi-randomized controlled trials. As per GRADE methodology, interventions were rated on the strength of recommendation and the quality of evidence. In the HELPinKIDS 2.0 guidelines, the authors took a rigorous approach in grading quality of evidence and this often resulted in reporting high levels of uncertainty in the evidence.

Technical consultation at WHO

A technical consultation was held on 16-17 February 2015 at WHO HQ in Geneva in order to determine if, how and which of the HELPinKIDS 2.0 recommendations could be adapted to WHO recommendations. Importantly, the technical consultancy group was tasked with not only adapting recommendations from a high-income setting to lower income settings, but were also adapting clinical practice guidelines to guidelines for public health programs and policy. Three authors of the HELPinKIDS 2.0 CPG attended. As well, an expert in immunization and/or pain was invited from each WHO region; disciplines covered included psychology, nursing, pharmacy, medicine, pain research, vaccinology and immunization program management.

Choice of interventions

Prior to the technical consultation, participants of the technical consultation were provided with the entire review of evidence and guidelines from HELPinKIDS 2.0 CPG. To facilitate the proceedings of the technical consultation three members of the SAGE Secretariat independently ranked the most globally relevant recommendations out of 55 separate interventions addressed by HELPinKIDS 2.0 and relating to physical, psychological, pharmacological, procedural, or process interventions (these include 44 for the treatment of pain and of individuals undergoing vaccine injections, five process interventions and an additional six interventions for the treatment of fear in people with high levels of needle fears- the latter were considered out of scope for the development for the global guidelines). Then by consensus, the SAGE Secretariat and the three authors of the CPG prioritized interventions considered to be most globally relevant including for LMIC based on feasibility and cultural acceptability for discussion and adaptation during the technical consultation (in some cases by collapsing multiple recommendations into one more general intervention).

These prioritized interventions were:

1. no aspiration,
2. injecting the most painful vaccine last,
3. positioning (holding infant/child, sitting up, parental presence),
4. breastfeeding before and during vaccine injection,
5. topical anaesthetics,
6. sweet tasting solutions for infants,
7. distraction,
8. education of clinicians regarding vaccine injection pain and fear management, and
9. education of caregivers and individuals regarding injection pain and fear management.

The latter two interventions were later considered as part of the implementation process of other interventions rather than self-standing interventions and are reflected accordingly in this document. An example of an intervention not prioritized for discussion included simultaneous injections as this was considered as impractical as it requires two health care providers working at same time.

During the technical consultation, detailed evidence for each of the prioritized interventions was presented and the considerations leading to them being recommended in the Canadian guidance document. The group then discussed the appropriateness of adapting each intervention to a global context considering cultural appropriateness, impacts on equity, availability, feasibility, acceptability, cost, and consistency with other WHO policies and recommendations (i.e., breastfeeding, nutrition, pain management, and injection practices).

Time was allotted during the technical consultation to systematically consider:

1. interventions that should explicitly be or not be recommended,
2. interventions where evidence was not clear enough to recommend them globally,
3. other interventions identified in the HELPinKIDS 2.0 project and not prioritized for discussion, and
4. other possible interventions not examined in the HELPinKIDS 2.0 but could be of use to mitigate pain during the vaccination event.

As a result additional interventions were added to the discussion (e.g., oral analgesics - see below).

Adaptation of the Canadian guidelines to WHO recommendations

In order to facilitate the adaptation of the Canadian clinical practice guidelines to WHO recommendations, group members were advised to consider the following questions, which were adapted from the evidence to decision *GRADE_DECIDE* guideline adaptation process (PLOS Medicine, in press):

<u>Benefits and harms</u>

- Are the identified benefits and harms relevant in the global context?
- Are there any additional benefits and harms that have not been considered?
- Are the benefits large compared to the harms?

<u>Resource use and value for money</u>

- What resources are required to implement this intervention (including human and monetary)?
- Are the costs worth the benefits?
- Are there any opportunity costs (i.e. by choosing this intervention, what opportunities are we giving up)?

<u>Impacts on equity</u>

- Would the intervention increase, decrease, or have no effect on health inequities?

<u>Acceptability</u>

- Is the intervention acceptable for patients, parents and health care workers?
- Are there any anticipated cultural barriers to this intervention?"

<u>Feasibility (implementability)</u>

- Is the intervention feasible to implement?
- If any special materials are required for this intervention, how feasible is it to procure them?

Other

- Are there are any other issues to consider (e.g. any other relevant WHO policy recommendations)?

Formulating recommendations on interventions

The technical consultation group agreed by consensus that there was no need to update the relevant and recently conducted systematic review from the HELPinKIDS 2.0 project as it was both exhaustive and recent (last date for update of literature: Feb 26 2015). The group adapted and recommended a number of interventions for inclusion in health policy and public health programs to reduce pain, distress and fear during vaccination. The interventions were categorized by WHO age group as "*all ages,*" *"infants," "children," "adolescents," or "adults (including pregnant and breastfeeding women)."*[ii] Some interventions were subcategorized under "conditional recommendations" in order to distinguish them as interventions which were recommended but may or may not be feasible or practical depending on context.

A list of interventions explicitly not recommended by the group was also determined, and again categorized by age. These interventions were further subcategorized as *"effective but not practical," "unknown effectiveness," "ineffective,"* or *"ineffective with potential harms."* Practicality of an intervention encompassed multiple issues, including resource use, feasibility and acceptability.

Implementation and research questions

The technical consultation group formulated a number of recommendations for WHO and countries to ensure the successful implementation of the interventions. Furthermore, a number of research questions that would be helpful in informing future recommendations were identified and those most important from a global perspective prioritized.

Examination of the evidence

As described above, based on the preliminary evaluation of benefits and harms, cultural acceptability and feasibility, a subset of the interventions included in 55 clinical questions in the HELPinKIDS guideline prioritized in-depth review at the technical consultation group meeting. The focus of the discussion was global feasibility and acceptability, in particular for Low and Middle Income Countries. In some cases multiple interventions were collapsed in one more general recommendation.

The evidence on the benefits and harms for each of the interventions is taken directly from the 2015 HELPinKIDS Guideline (noted in quotation marks and italics) and as a result is categorized according to Canadian age groupings for which the relevant cut-offs may depart from that of WHO e.g. for adolescents as well as according to availability of the evidence. The specific 2015

[ii] Infants 0-11 months, children 1-9 years, adolescents 10-19 years

HELPinKIDS Guideline recommendation to which the passage refers is noted at the end of the quote. The source of the evidence is mentioned in each section but the specific references are not added in the list of references at the end of this document. For the complete list of references, please refer to the HELPinKIDS guideline posted on the SAGE website.

1. No aspiration

Aspiration i.e. pulling the syringe plunger before intramuscular injection to see if blood is aspirated is a long-standing practice in certain geographical areas that was initially proposed for safety reasons, i.e. to prevent injection in blood vessels.

Evidence: "*Aspiration may add to pain because of longer contact time and lateral movement (wiggling) of the needle*. *Three studies including individuals from infancy to adulthood were included in the systematic review (Girish et al., 2014, Ipp et al., 2007; Petousis-Harris et al., 2013). There was very low quality evidence for pain and distress (critically important outcomes) due to risk of bias and imprecision. In the single study that included 114 individuals able to provide self-report (Petousis-Harris et al., 2013, no evidence of a difference in pain between aspiration and no aspiration groups was demonstrated. In the two studies including 313 infants, there was a benefit of not aspirating on infant acute distress (Girish et al., 2014, Ipp et al., 2007): SMD -0.82 (95% CI -1.18, -0.46). The latter studies, however, were confounded by the speed of injection (i.e., slow injection speed for the aspiration group compared to a fast injection speed for the no aspiration group)*." (HELPinKIDS 2.0 CPG Recommendation 1).[3] The lack of benefit of not aspirating in the Petousis-Harris (2013) study may be due to: 1) a ceiling effect (peak pain experienced in both groups as soon as the vaccine was injected due to the high degree of pain from the vaccine used itself), 2) a floor effect (minimal difference in pain among techniques because of the small differences in duration of administration time between them), 3) age/participant-related effects (unclear what participants knew about the study and how this impacted their ratings of pain), or 4) a confounder (the authors describe that some vaccines were injected in a different anatomical site than intended and were potentially more painful. This probably occurred in the quick injection group and not the other groups).

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: Benefits of no aspiration include shorter contact time with the needle and reduced potential for lateral movement (wiggling) of the needle, leading to less pain. There are no established harms.

Resource use and value for money: No additional resources are required for implementation other than education of providers.

Impacts on equity: There are no anticipated impacts on health inequity.

Acceptability: No concerns were expressed regarding the cultural acceptability of not aspirating.

Feasibility (implementability): The intervention was seen as highly feasible.

Other: If the anatomical site for injection is chosen correctly, aspiration is not necessary; this is because recommended injection sites are not near major vessels. It is important to note that slight bleeding after withdrawal of the needle does not indicate penetration of blood vessels, as minor

surface vessels can be perforated during injection. The WHO recommends the exclusive use of auto-disable (AD) syringes for vaccinations so that they cannot be reused and most of these syringes do not allow for aspiration. Most LMIC follow this recommendation whereas most HIC do not. From this vantage point, LMIC are better equipped to reduce pain from vaccination because their syringes do not allow for aspiration.

2. Administer vaccines in order of increasing painfulness

Evidence*: "During many visits for routine childhood immunization visits, more than one vaccine injection is administered. It is known that some vaccines cause more pain during injection than others. Two studies including infants from 0 to 6 months were included in the systematic review (Ipp et al., 2009; Ravikiran et al., 2011). There was moderate quality evidence for distress, the critical outcome due to imprecision, and evidence of a substantial benefit when the most painful vaccine was injected last. Included studies compared either: 1) pneumococcus conjugate vaccine, PCV (Prevnar™) to diphtheria and tetanus toxoids, polio, acellular pertussis, and Haemophilus influenzae type b conjugate vaccine, DPTaP-Hib (Pentacel™), or 2) BCG vaccine (TUBERVAC™) to hepatitis B vaccine (GeneVac-B™). PCV and hepatitis B caused lower overall infant acute distress (n=196) when given last: SMD -0.69 (95% CI -0.98, -0.40). No studies were identified that included individuals able to self-report pain.)."* (HELPinKIDS 2.0 CPG Recommendation 2).[3]

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: There are clear, positive benefits and no anticipated harms.

Resource use and value for money: No additional resources are required for implementation other than education of providers.

Impacts on equity: There are no anticipated impacts on health inequity.

Acceptability: No concerns were expressed regarding the cultural acceptability of administering vaccines in order of increasing painfulness.

Feasibility (implementability): A significant limitation to implementing this intervention is that we do not yet have a way to rate the painfulness of different vaccines at the time of injection as this is not required information for licensure, and therefore are currently unable to advise vaccine administrators on the order in which vaccines should be administered. Health care workers may "know" which is the most painful vaccine through experience but no standardized comparative evaluations of pain at the vaccination event across different vaccines and different preparations is available. For vaccines for which painfulness is very similar and cannot be distinguished from experience, the order of sequencing likely is of no consequence. Based on feed-back from the field, global guidance on how to sequence vaccines or categories of vaccines could hopefully be provided in the near future for prequalified vaccines.

Other: Administering vaccines in order of increasing painfulness may prevent pain sensitization.

3. Positioning

Evidence: "*The intervention of positioning includes holding children <=3 years of age as well as having all those over 3 years and adults sit up when receiving vaccinations. Individuals may be*

positioned in a number of different ways (e.g. sitting up, supine, etc.). Some positions are more comfortable and promote a greater sense of control."

Holding for those up to 3 years of age

Evidence: *"Three studies including 213 infants aged 6 weeks to 6 months were included in the systematic review (Hallstrom 1968; Ipp, Taddio et al., 2004; Taavoni et al., 2010). The intervention consisted of holding of the infant by a parent. Holding was initiated before vaccine injection(s) and continued during and after injection(s). There was low to very low quality of evidence across the different indicators of infant distress (critical outcome) due primarily to risk of bias from lack of blinding and imprecision, and there was no evidence of a benefit of holding. In the only analysis that included all studies (n=213), there was no evidence of a benefit on acute infant distress. However, there was contamination of the control (lying supine) group (i.e., some infants in the supine group were picked up and held immediately afterwards) in one of the studies (Ipp, Taddio et al., 2004). Removal of the data from this study led to a benefit in acute distress: SMD -1.25 (-2.05, -0.46). The results were not significant for the other distress outcome (i.e., acute and recovery phase); however, the data were obtained from the same flawed study (i.e., Ipp, Taddio et al., 2004)*." (HELPinKIDS 2.0 CPG Recommendation 9).[3]

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: Evidence shows that holding a child aged up to 3 years helps alleviate some distress, and the child may be held by any caregiver, not just the parent. There are no anticipated harms.

Resource use and value for money: At minimum a chair is recommended for the person holding the child to increase comfort and promote safety (minimize risk of falls).

Impacts on equity: There are no anticipated impacts on health inequity.

Acceptability: No concerns were expressed regarding the cultural acceptability of positioning. In some African countries, parents and children are very used to being watched while being immunized and positioning the child is not a problem from this perspective.

Feasibility (implementability): This intervention was seen as highly feasible. However, health workers will need to be trained on the implementation of this intervention on best positioning as well as how to best advise parents in a courteous manner as this latter aspect will also be important. Health care workers may need to adjust their own positioning in order to deliver vaccinations in a comfortable and safe manner.

Other: None

Sitting up during vaccine injections should be used in children over 3 years and in youth and adults

Evidence: *"One study including children aged 4 to 6 years was included in the systematic review (Lacey et al., 2008). There was low quality evidence for critical outcomes (fear, pain) due to risk of bias and imprecision. The results were mixed: a benefit was observed for fear [n=107; SMD -0.39, 95% CI -0.77, -0.01)] but not for pain (SMD: 0.07, 95% CI -0.31, 0.45). We considered the results for distress given that the children were of an age where self-report may not be reliable (Chambers 2002,*

von Baeyer, Forsyth et al., 2009). Both measured distress outcomes demonstrated a benefit of the intervention. There were no identified undesirable consequences." (HELPinKIDS 2.0 CPG Recommendation 11).[3]

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: Evidence shows that sitting up for those over 3 years and youth/adults may help alleviate fear and distress. For younger children this can be done sitting on a parent's lap in a hug with child's legs on either side of the parent's lap and parent's arms over the child's arms to help the child to stay still. Older children, youth and adults sit on their own. Lying down may be preferred in those with a history of fainting; providing support or reclining may avoid falls from a seated position. There are no anticipated harms.

Resource use and value for money: At minimum a chair is required for the person receiving the vaccination or holding the young child. Alternatively, one could sit on the ground.

Impacts on equity: There are no anticipated impacts on health inequity.

Acceptability: No concerns were expressed regarding the cultural acceptability of positioning. In some African countries, parents, children and adults are very used to being watched while being immunized so positioning is not seen as a problem from this perspective.

Feasibility (implementability): This intervention was seen as highly feasible. However, health workers will need to be trained on the implementation of this intervention as the courtesy with which health care workers advise parents, children and adults on positioning will likely be very important. Health care workers may need to adjust their own positioning in order to deliver vaccinations in a comfortable and safe manner.

Other: None

4. Use of language to reduce pain and fear: neutral verbal cues for impending vaccination, repeated reassurance, and false suggestions of minimal pain

Evidence: "*When communicating with individuals during painful procedures, the use of language that is unnecessarily highly negative in valence has been discouraged. Similarly, providing false suggestions about the amount of pain involved (i.e., minimizing pain or lying about pain) and excessive use of reassurance are not generally recommended. Together, the use of these interventions have not been shown to reduce pain and may even increase pain. In the case of false suggestions, there is the potential to promote distrust."* (HELPinKIDS 2.0 CPG).[3]

False suggestions of minimal pain

Evidence: *"Two studies including 240 children aged 4 to 6 were included in the systematic review (Eland, 1981; Fowler-Kerry & Lander, 1987). In both studies, children were given a placebo intervention (i.e., wearing headphones or air sprayed on the skin at the injection site) and told by the experimenter or clinician that something was being done to help them during the injection or to make the injection hurt less. Both studies examined the impact of adding suggestion to another intervention (i.e., distraction or vapocoolants) as well. There was low quality evidence for the critical outcome (pain) due to risk of bias (inconsistent or lacking of blinding and selective outcome reporting)*

and imprecision and no evidence of a benefit on pain. Since the inclusion of pain-relieving interventions with suggestions confounds the issue, the analysis was repeated excluding the data for pain-relieving interventions. The results were not altered. There was no evidence for the critical outcome of fear." ((HELPinKIDS 2.0 CPG Recommendation 30).[3] As previously stated, *"The use of false suggestions of minimal pain (e.g., "it's just a poke") and lies (e.g., "it won't hurt") may promote distrust between any individual delivering such messages and individuals undergoing vaccination (Taddio, Ilersich et al., 2014)."*

Repeated reassurance

Evidence: *"Two studies (Gonzalez et al., 1993; Manimala et al., 2000) including 82 children aged 3 to 7 years were included in the systematic review. In both studies, repeated reassurance by the parents was examined. Methods of training the parents in the use of reassurance varied between studies and included instructions, audio and live modeling, and practice; parents were also reminded throughout the procedure to use reassurance. There was very low to low quality evidence for critical outcomes (pain, fear) due to risk of bias and imprecision. There was no evidence of a benefit of reassurance in critical outcomes. There was very low quality of evidence for distress (important outcome) and no evidence of a benefit."* (HELPinKIDS 2.0 CPG Recommendation 31).[3]

Verbal signal about pain

Evidence*: "Three studies including 391 adults undergoing venipuncture (Ott et al., 2012; Vijayan et al., 2015) or IV cannulation (Dutt-Gupta et al., 2007) were included in the systematic review. In all studies, individuals were given a verbal signal about the start of the procedure or a signal about the pain. One study specifically excluded individuals with significant needle fears (Ott et al., 2012). Data were available for the critical outcome of pain but not fear. For the critical outcome of pain, there was very low quality evidence due to risk of bias, indirectness, and imprecision, and no evidence of a benefit of the intervention." Despite the lack of observed benefit, it is recommended that more neutral warnings or prompts about the procedure (e.g., "Here I go") be used."* (HELPinKIDS 2.0 CPG Recommendation 29).[3]

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: Discussion with individuals undergoing vaccination and signalling the impending procedure is a routine part of the vaccination process to try to minimize sudden movements and elicit coping strategies in individuals. Evidence suggests that the use of language that enhances anxiety or is falsely reassuring or dishonest is not beneficial and may harm by increasing distress and decreasing trust. Separately, it has been demonstrated that threatening words undermine pain-relieving interventions.[22,28] Neutral language is preferred. There is strong rationale across childhood for avoiding repeated reassurance. This recommendation applies to children of all ages as even if they are too young to understand the words, they may understand the tone of voice (which is hypothesized to be important to the effect of this intervention). Indeed repeated reassurance has been demonstrated in observational studies to be associated with higher distress in babies. There are less data for adults, but there is rationale to avoid excessive reassurance as repeatedly saying statements like 'don't worry it will be over soon' are expected to be at least not helpful and potentially anxiety-provoking in older age groups. False suggestions about pain are to be avoided across the lifespan as they promote distrust. Note that even if the person getting immunized is a baby, parents will hear these messages and may become untrusting.

Resource use and value for money: The only additional resources required are that required to build messages on the use of language into existing education and training programs for healthcare workers.

Impacts on equity: There are no anticipated impacts on health inequity.

Acceptability: No concerns were expressed regarding cultural acceptability.

Feasibility (implementability): This intervention was seen as feasible. However, health workers will need to be trained on the implementation of this intervention as use of neutral words and avoidance of anxiety provoking language is not necessarily widely done routinely.

Other: None

5. Caregiver presence

Evidence: Children are vaccinated in different settings and parents may or may not always be present. "*Four studies including 245 children aged 13 months to 9 years were included in the systematic review (Broome & Endsley, 1989; Gonzalez et al., 1989; O'Laughlin & Ridley-Johnson, 1995; Shaw & Routh, 1982). Parents were present (were not provided with any training with how to behave) or absent during their children's vaccinations. There was very low quality evidence for important outcomes (distress in individuals unable to provide self-report, child preferences) and no data for critical outcomes (pain, fear). Extensive selective reporting bias, lack of blinding and a small sample size contributed to the quality rating. Results were mixed for different indicators of distress. Available evidence showed a strong preference by children to have their parents present (Gonzalez et al., 1989).*" (HELPinKIDS 2.0 CPG Recommendation 46).[3]

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: In general there is a dearth of literature around examining the benefits of having a caregiver present for vaccination. This is likely because in many high income countries such as Canada the assumption is that parents should/will be present, and research has instead focused on what parents are doing when present during vaccinations. Child preference should be attended to (e.g., occasionally fear on the part of a caregiver may accentuate fear for the child who thus may wish the caregiver not to be present).

Resource use and value for money: No additional resources are required for implementation as all infants and young children are accompanied by a caregiver for vaccinations.

Impacts on equity: There are no anticipated impacts on health inequity.

Acceptability: No concerns were expressed regarding the cultural acceptability of having a caregiver present. In Thailand, guardian presence is a must but it does not have to be a parent; often an extended relative accompanies the infant or young child.

Feasibility (implementability): This intervention is highly feasible for infants. In some countries such as Belgium, school-based vaccination starts around 6 years of age so parents are not present. Therefore, this recommendation has been limited to the pre-school age.

Other: None

6. Breastfeeding

Evidence: *"Breastfeeding is one of the most significant factors in promoting optimal health and development in children and is the normative standard for infant feeding and nutrition (Gregory et al., 2014). Within the context of vaccination, there is evidence that breastfeeding may improve the effectiveness of some vaccines and reduce fever associated with vaccine injections (Dórea 2012; Pisacane et al., 2010).*

For the 2015 HelpinKids Guideline*, breastfeeding was specifically evaluated for its effectiveness in reducing distress in young children during 2 different time points relative to vaccine injections: 1) during needle puncture and administration of the vaccine and 2) beforehand (i.e., before needle puncture and administration of the vaccine. When used during vaccine injections, breastfeeding is hypothesized to reduce distress via multiple mechanisms, including: physical comfort, sucking, distraction and ingestion of sweet-tasting and other substances that may have individually and together, have pain and distress-relieving effects. When used before vaccine injections, breastfeeding may reduce distress via satiation of infants, which may promote calmness during needle procedures.*

Previous systematic reviews have demonstrated the effectiveness of breastfeeding undertaken during needle procedures in neonates and infants (Shah et al., 2009, Shah et al., 2012) and breastfeeding is used in hospital settings to reduce needle-related pain (Foster et al., 2013)." (HELPinKIDS 2.0 CPG).[3]

Breastfeeding at time of vaccination

Evidence: *"Nine citations that included data from 8 separate studies that examined breastfeeding* ***during*** *vaccination were included in the systematic review (Dilli et al., 2009; Efe & Özer, 2007; Goswami et al., 2013; Iqbal et al. 2014; Modarres et al., 2013; Abdel Razek & El-Dein, 2009; ShahAli et al., 2009; Taavoni et al., 2009 (same study as ShahAli et al., 2009); Thomas et al., 2011). Seven trials including 792 infants reported data for acute distress (Dilli et al., 2009; Goswami et al., 2013; Iqbal et al. 2014; Modarres et al., 2013; Abdel Razek & El-Dein, 2009; Shah Ali et al., 2009; Taavoni et al., 2009; Thomas et al., 2011). The quality of evidence for this outcome was low, downgraded for risk of bias due to lack of blinding and lack of consistent randomization across included studies. The SMD was -1.78 (95% CI -2.35, -1.22). The other distress outcomes included between one and four studies and all demonstrated a benefit of breastfeeding. The nature of the intervention prevents blinding and the sample size was small for some of the distress outcomes. The magnitude of benefit is substantial and valued highly".* (HELPinKIDS 2.0 CPG Recommendation 6).[3]

Breastfeeding before vaccination

Evidence: "*Two trials including 100 infants aged 6 weeks to 3 months investigated the effect of breastfeeding* ***before*** *vaccine injections (Achema et al., 2011; Sahebihagh et al., 2011). The timing when breastfeeding ended was 2 minutes to 1 hour before vaccination. There was moderate to low quality evidence across all distress outcomes (critical outcome) due to risk of bias and imprecision. In the only analysis that included data from both studies, acute distress was lower in the infants in the*

breastfeeding group: SMD -1.43 (-2.14, -0.72). The results were mixed for other distress outcomes." (HELPinKIDS 2.0 CPG Recommendation 7).[3]

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: There are significant benefits to breastfeeding as WHO recommends exclusive breastfeeding for the first six months of life and that thereafter infants should receive complementary foods with continued breastfeeding up to 2 years of age or beyond.[23,24] Therefore, there is a synergistic potential for this recommendation to align with those of infant nutrition. There are no known harms to breastfeeding. HIV infected mothers should be counselled to exclusively breastfeed in the first six months of life and continue breastfeeding thereafter unless environmental and social circumstances are safe for, and supportive of, replacement feeding. In circumstances where antiretrovirals (ARVs) are unlikely to be available, such as acute emergencies, breastfeeding of HIV-exposed infants is also recommended to increase survival.[25]

Resource use and value for money: No additional resources are required for breastfeeding. Allowing time for a mother to breastfeed may be a constraint. Health care workers will need to be trained on being courteous and supportive of this intervention.

Acceptability: Breastfeeding in public is culturally acceptable in some places, such as Ghana, but not in others, such as Thailand. Furthermore, women may not want to breastfeed in front of male health care workers. For these reasons, this intervention can only be conditionally recommended.

Feasibility (implementability): WHO recommends exclusive breastfeeding until 6 months of age and that thereafter infants should receive complementary foods with continued breastfeeding up to 2 years of age or beyond, however many women do not breastfeed that long. It should be noted that sucking does not always occur spontaneously at the moment needed.

Other: Bottle-feeding (with pumped breast milk or use of formula) should have a similar effect as it closely mimics breastfeeding (holding, sweet tasting solution, sucking) but water supplies are not safe in all parts of the world. As stated above, WHO recommends exclusive breastfeeding for the first six months of life and that thereafter infants should receive complementary foods with continued breastfeeding up to 2 years of age or beyond. Therefore, bottle-feeding is not recommended universally as an intervention. However, if the child is already bottle-feeding at home then this is an appropriate intervention.

7. Sweet solutions

"*Sweet-tasting solutions (sucrose solutions and glucose/dextrose solutions) have been extensively evaluated for their analgesic and calming effects in infants undergoing needle procedures (Harrison et al., 2012). The mechanism of action of sweet-tasting solutions is not known but may involve release of endogenous opioids and distraction. Sweet-tasting solutions are commonly used in hospital settings to reduce distress in infants undergoing various types of aversive medical procedures (Taddio, Yiu, et al., 2009; Foster et al., 2013).*" (HELPinKIDS 2.0 CPG).[3]

Sweet-tasting solutions are usually given by syringe; however they can also be administered by dropper, cup or bottle. The effect is immediate and lasts at least five minutes which is long enough

to administer multiple injections. The upper age for the effect is unknown most studies have investigated the effectiveness of sweet-tasting solutions in the first 12 months of life.

Sucrose

Evidence: *"Eighteen studies were included in the systematic review* of sucrose solutions *including children in the first 19 months of life (Allen et al., 1996; Barr et al., 1995; Chattopadhyay et al., 2011; Dilli et al., 2009; Harrison et al., 2014; Hatfield, 2008; Hatfield et al., 2008a; Harrington et al., 2012; Lewindon et al., 1998; Liaw et al., 2011; Moradi et al., 2012; Mowery, 2007; Poulsen, 2009; Priambodo et al., 2008; Ramenghi et al., 2002; Sahebihagh et al., 2011; Soriano Faura & Gomez, 2003; Yilmaz et al., 2014). The sucrose concentrations evaluated ranged from 12% to 75% in all but one study, which described using a saturated solution. The volume used was 2 mL in all but three studies (others used 0.75 mL or 0.6 mL/kg) and the usual timing of administration was 1-2 minutes prior to injection. Across all distress measures (critically important outcome), the quality of evidence was high to moderate. The results were positive for 4 out of 5 measures of distress. In the analysis including the largest number of studies (n=2071 infants and children), there was a benefit for distress in the acute and recovery period combined: -0.76 (95% CI -1.19, -0.34). Sub-group analyses were undertaken for 3 of the distress outcomes; they demonstrated a dose-response relationship, with concentrations above 20% sucrose (weight/volume) appearing to be the cut-off for observable benefit."* (HELPinKIDS 2.0 CPG Recommendation 22).[3]

Glucose

Evidence: "*Six studies investigating glucose (dextrose) for vaccine injections including infants in the first 12 months of life were included in the systematic review (Chermont et al., 2009; Golestan et al., 2007; Goswami et al., 2013; Morelius et al., 2009; Kassab et al., 2012; Thyr et al., 2007). In included studies, the concentration of glucose ranged from 25% to 50% and the volume administered ranged from 1 - 2 mL. The timing of administration was variable: 2 minutes before injection (3 studies: Chermont et al., 2009; Golestan et al., 2007; Goswami et al., 2013), immediately before (2 studies: Kassab et al., 2012; Morelius et al., 2009), and 30 seconds before/during/10-30 seconds after (1 study: Thyr et al., 2007). There was high to moderate quality of evidence across the critical outcomes of distress; the quality was downgraded due to inconsistent blinded across studies. The results were mixed for different indicators of distress. In the only analysis that included all of the studies (n=818), there was a benefit of glucose on acute and recovery distress combined: SMD -0.69 (95% CI -1.03, -0.35)."* (HELPinKIDS 2.0 CPG Recommendation 23).[3]

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: There is good evidence of benefit of sweet-tasting solutions in infants not breastfed during vaccine injections. Furthermore, programs may be able to make use of rotavirus oral vaccine as the sweet-tasting solution since it contains sucrose (see Table 1 below). It is important to note, however, that the concentration of sucrose varies considerably among products available or in development and the minimal concentration that is required for analgesia is not known. At present, only one brand containing 71.5% sucrose has been demonstrated not to differ significantly in its analgesic effects compared to sucrose 24%.[26] Risk of dental caries and interference with breastfeeding are not considered harms as these are one-off interventions.

Table 1: Sucrose Concentrations in Different Rotavirus vaccines

	Concentration of Sucrose considered sufficient for Pain Mitigation	**Concentration of Sucrose considered insufficient for Pain Mitigation**
Prequalified vaccines		
GSK Rotarix™, Belgium Liquid	1.5 ml (1 dose) contains: • Sucrose: 1073 mg • Concentration: 71.5%	
GSK Rotarix™, Belgium Powder		After reconstitution, 1 ml (1 dose) contains: • Sucrose: 9 mg • Concentration of sucrose: 0.9%
Merck RotaTeq®, USA	2 ml (1 dose) contains: • Sucrose: 1080 mg • Concentration: 54%	
Vaccines in development		
Serum Institute of India – lyophilized vaccine		After reconstitution, 2.5 ml (1 dose) contains: • Sucrose: 50 mg • Concentration: 2%
Serum Institute of India – liquid vaccine	1 dose, 2ml contains: • Sucrose: 568 mg • Concentration: 28.4%	
Murdoch Children's Research Institute, Australia – RV3-BB		1ml contains: • Sucrose concentration: 10%
Biofarma, Indonesia	1 dose, 1 ml contains: • Sucrose concentration: 30%	
Bharat Biotech, India – ROTAVAC® licensed liquid formulation		0.5 ml (1 dose) contains: • Sucrose: 37.31 mg • Concentration: 7.5%
Instituto Butantan, Brazil – pentavalent rotavirus vaccine, lyophilized		0.5 ml (1 dose) contains: • Sucrose: 30 mg • Concentration: 6.0%

Resource use and value for money: Resources required include sucrose or glucose, clean water, device for administration (e.g. syringe, cup, bottle), time for preparation and training of health care workers. For these reasons, this intervention can only be conditionally recommended.

Impacts on equity: There are potential inequities if some are able to access this intervention while others are not.

Acceptability: No concerns were expressed regarding cultural acceptability. Sweet-tasting solutions are being used as a pain medicine, not as a food. It does not conflict with baby friendly initiatives.

Feasibility (implementability): This intervention would require training of health practitioners and/or caregivers. Sucrose would appear to be more feasible for people to prepare themselves or to be prepared on the spot by health care providers, but glucose is more readily available in hospital settings. Ensuring water is not contaminated would be a condition required for this intervention. However, in many parts of the world it is unlikely that all the supplies required for this intervention can be consistently and equitably procured. Sweet solutions >20% are generally effective; most commonly concentrations of 24-50% are used. There is no evidence of increased benefit with higher concentrations. One could use commercial solutions or prepare a solution with clean water (i.e., safe drinking water); in this instance use one packet of sugar (i.e. about one teaspoonful) mixed in 10 ml (i.e. two teaspoons) of water, and one should ensure that the sugar is fully dissolved, which should take no more than a couple of minutes (faster if stirred).

In places and for vaccination sessions where rotavirus vaccine is being co-administered with injectable vaccines and mothers are breast feeding, it would be best to recommend administration of the oral rotavirus, then oral polio vaccine (when OPV is used) first, then breast feeding, then injectable vaccines.

Other: Honey is not recommended as the sweet-tasting solution due to the risk of infant botulism and as per WHO guidance against feeding honey to infants <1 year of age.[27]

8. Topical anaesthetics

"*Topical anaesthetics are local anaesthetic-containing creams and gels that are applied to the skin and penetrate through the superficial layers to block transmission of nociception via Na+ channel blockade (McLure & Rubin, 2005). They are commonly used to treat pain from a variety of superficial skin procedures, including needle insertion, and have been demonstrated to be safe and effective in individuals of all ages, including young infants (Eidelman et al., 2005; Houck & Sethna, 2005; Taddio et al., 1998).*

Health care providers, caregivers of children undergoing vaccination and adults undergoing vaccination should be instructed on the application of topical anaesthetics, including location, dose and timing. Because currently available topical anaesthetics require between 20 and 60 minutes for adequate anaesthesia, it is necessary to plan for their use. They can be administered prior to arrival at the vaccination setting or upon arrival, depending on the usual waiting times and parent and/or individual preferences." (HELPinKIDS 2.0 CPG)[3]

The package instructions on how to apply these commercially produced products should be followed. Self-compounded preparations should never be used because they may either be ineffective or

dangerous (due to superficial skin irritation/damage or significant absorption through the skin and systemic toxicity).

Evidence: "*Sixteen studies including individuals from infancy to adulthood were included (Abuelkheir et al., 2014; Achema et al., 2011; Basiri-Moghadam et al., 2014; Cassidy et al., 2001; Cohen et al., 1999; Cohen et al., 2006; Dilli et al., 2009; Gupta et al., 2013; Halperin et al., 2000; Halperin et al., 2002; Hansen & Sorensen, 1993; Kumar 2014; O'Brien et al., 2004; Taddio et al., 1992; Taddio et al., 1994; Uhari, 1993). The majority of included studies (n=10) investigated topical anesthetics for intramuscular vaccine injections; and remainder of the six studies investigated subcutaneous injections (n=3; Hansen & Sorensen, 1993; Halperin et al., 2002; O'Brien et al., 2004); combination of intramuscular and subcutaneous injections (n=2; Abuelkheir et al., 2014; Cohen et al., 2006) and combination of intramuscular, subcutaneous and intradermal injections (n=1; Dilli et al., 2009).*

Topical anaesthetics for children up to 12 years of age

Evidence: "Fourteen studies were included in the systematic review including children in the first 12 years of life (Abuelkheir et al., 2014; Achema et al., 2011; Basiri-Moghadam et al., 2014; Cassidy et al., 2001; Cohen et al., 1999; Cohen et al., 2006; Dilli et al., 2009; Gupta et al., 2013; Halperin et al., 2000; Halperin et al., 2002; Kumar 2014; O'Brien et al., 2004; Taddio et al., 1994; Uhari, 1993). The majority of included studies were carried out in young children unable to provide self-report of pain. The quality of evidence ranged from moderate to very low. While the results were mixed for different indicators of distress, this was partly due to low sample sizes for analyses undertaken for some of the indicators and high risk of bias for some studies. In the analysis with the largest number of included studies (n=1424 children), there was a substantial benefit of topical anaesthetics on acute distress: SMD -0.91 (-1.36, -0.47). Two studies reported data for pain (Cassidy et al., 2001; Cohen et al., 1999). The quality of the evidence was moderate to very low due to risk of bias and imprecision. Without the data from one study with a high risk of bias (Cohen et al., 1999), there is high quality evidence and a benefit was observed for pain: SMD -0.47 (-0.78, -0.16). One study of very low quality included data for fear (critical outcome) for 68 children (Cohen et al., 1999). There was no evidence of a benefit of this intervention for this outcome." (HELPinKIDS 2.0 CPG Recommendation 17).[3]

Topical anaesthetics for adolescents >12 years and adults

Evidence: "Two studies including adolescents and adults were included in the systematic review (Hansen & Sorensen, 1993; Taddio et al., 1992). There was moderate quality evidence for the critical outcome of pain. In the single study included in the meta-analysis for critical outcomes (Taddio et al., 1992) with 60 participants, there was a benefit of the intervention: SMD -0.85 (95% CI -1.38, -0.32)." (HELPinKIDS 2.0 CPG Recommendation 18).[3]

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: There is good evidence of benefit. Topical anaesthetics can be used for both subcutaneous and intramuscular injections. Furthermore, up to three injections can be administered in the surface area covered by one patch. There is no evidence of an effect of topical anaesthetics on immune response to vaccines.[3]

A potential harm is the possibility of people self-compounding preparations, which may be ineffective or dangerous due to the risk of superficial skin damage or systemic toxicity. Therefore,

only commercially-available preparations specifically indicated for injection pain should be applied and package instructions followed.

Resource use and value for money: The cost of topical anaesthetics is a major concern. Some people in HIC and MIC may be willing and able to pay for topical anaesthetics; however this intervention is difficult or unattainable for others (especially in LIC). In some LIC, the cost of topical anaesthetic is much more than the cost of the vaccination itself.

Impacts on equity: Topical anaesthetics are not available globally, regardless of willingness to pay. In areas where they are available, there are major impacts on health equity given that some people are not able to afford this intervention. While people should have the option to avail of it, given its inequitable access around the world, the WHO cannot recommend this intervention globally.

Acceptability: There are no concerns about the acceptability of the use of topical anaesthetics. Given that vaccinations are regarded as a free health service in LIC, it would not be acceptable to recommend an intervention for which an individual would have to pay.

Feasibility (implementability): In some countries a prescription is required while in others the products are available over-the-counter. Topical anaesthetics require education to ensure proper application, as well as advanced planning and relative certainty of the time of injection given that it must be applied 20-60 minutes prior to vaccination. Health care providers administering vaccinations, caregivers of children undergoing vaccination and individuals undergoing vaccination would need to be educated about this intervention.

Other: While use should follow the product monograph, it is noted that independent studies have demonstrated that topical anaesthetics are safe and effective, even in newborn infants although the product monograph still advises that use be limited to >3 months of age. The interaction of this preparation with the immune response has been evaluated for some vaccines with no evidence of harm (i.e., no interference with antibody response). We have extrapolated their safety in this regard for all vaccines.

9. Distraction

"Distraction involves the use of strategies to divert an individual's attention away from pain to something more pleasant. Distraction may reduce pain by engaging neural mechanisms that facilitate endogenous modulation of pain (Bandura et al., 1988; Valet et al., 2004) as well as decreasing attentional resources that would otherwise be allocated to processing of pain (Johnson, 2005). There may be substantial individual differences in the effectiveness of distraction for pain reduction (Van Damme et al., 2010). Distraction may be more effective for individuals whose typical coping style involves disengaging (Verhoeven et al., 2012; Piira et al., 2006; Fanurik et al., 1993) rather than attending to the source of pain and also for those who have a low fear of pain (Roelofs et al., 2004).

Distraction can be achieved using a variety of 'distractors'. In children, this typically includes toys, videos, and music. However, distraction can also involve conversation with an adult. Distractors that are very engaging, interactive, and intrinsically interesting are believed to be more effective (Cohen 2008). Distraction is typically commenced before the procedure begins, and is continued during and afterwards - this is believed to reduce anticipatory anxiety, pain, and to enhance recovery, respectively (Cohen 2008). Recent systematic reviews demonstrate some benefit of distraction for reducing pain during needle procedures, including vaccination, in children (Birnie et al., 2014; Pillai Riddell et al., 2014; Uman et al., 2013).

In general, the ability to intentionally and capably engage in self-regulatory processes improves with age and individuals become less reliant on external sources (e.g., distractors) to cope with pain (Skinner & Zimmer-Gembeck, 2007). Adults may be more likely to engage in cognitive distraction, in which they can distract themselves effectively merely by thinking about other things." (HELPinKIDS 2.0 CPG).[3]

The distractions examined for these global recommendations included music, videos, toys, breathing interventions, verbal and visual distraction.

Toys: for infants and very young children (up to 3 years)

Evidence: "*Five studies including 549 children aged 2 months to 3 years were included in the systematic review that investigated directed toy distraction (Cramer-Berness 2005; Cramer-Berness & Friedman, 2005a; Gedam et al., 2013; Hillgrove-Stuart et al., 2013; Singh, 2012). In three of them, parents were instructed in distraction. There was low to very low quality evidence across the critical outcomes of distress due to risk of bias with or without imprecision. The results were mixed; a benefit was demonstrated for distress pre-procedure, acute and recovery combined in one study [n=81; SMD -0.47 (95% CI -0.91, -0.02)]. In the only analysis that included all 5 studies (n=549), there was no evidence of a benefit for acute distress: SMD -0.94 (95% CI -1.98, 0.10).* (HELPinKIDS 2.0 CPG Recommendation 33).[3]

Four studies including children aged 2 months to 3 years were included in the systematic review that investigated non-directed toy distraction (Basiri-Moghadam 2014; Cramer-Berness, 2005; Ozdemir & Tufekci 2012; Singh, 2012). The methods of distraction included toys and mobiles. There was low to very low quality of evidence due to risk of bias and imprecision for the critical outcome (distress) and the results were mixed for different indicators of distress. In the only analysis that included all 4 studies (n=290), there was a benefit for acute distress: SMD -0.93 (95% CI -1.86, 0.00). (HELPinKIDS 2.0 CPG Recommendation 34).[3]

The evidence base for toy distraction in children > 3-12 years is presented under Breathing Interventions (below).

Music: For children >3-12 years

Evidence**: "***Four studies including children aged 3 to 7 years were included in the systematic review (Fowler-Kerry & Lander, 1987; Megel et al., 1998; Noguchi, 2006; Yinger 2012). There was low quality evidence due to risk of bias and imprecision. There was evidence of a benefit for pain: in the analysis including all the largest number of studies (n=361), the SMD was -0.45 (95% CI -0.71, -0.18). There was no evidence for the critical outcome of fear."* (HELPinKIDS 2.0 CPG Recommendation 37).[3]

Music: For adolescents >12-17 years

Evidence**: "***One study including adolescents 13 to 15 years was included in the systematic review (Kristjánsdóttir & Kristjánsdóttir, 2011). There was low quality evidence due to risk of bias and no evidence of a benefit: [(n=118): SMD -0.04 (95% CI -0.42, 0.34). There was no evidence for the critical outcome of fear."* ((HELPinKIDS 2.0 CPG Recommendation 38).[3]

Music: For Adults

Evidence: *"No studies were identified specific to vaccine injections. Two studies including 156 adults undergoing venipuncture were included in the systematic review (Jacobson, 1999; Jacobson, 2006). In both studies, individuals self-selected from a variety of options. There was very low quality evidence for critical outcomes (pain, fear) due to risk of bias, indirectness and imprecision and no evidence of a benefit for both critical outcomes*." (HELPinKIDS 2.0 CPG Recommendation 39).[3]

Video: For infants and very young children (up to 3 years)

Evidence: **"***Four studies including 512 children aged 1 month to 3 years were included in the systematic review (Cohen, 2002; Cohen, Bernard et al., 2006; Cohen, MacLaren et al., 2006a; Gedam et al., 2013). In three of the studies, nurse immunizers were instructed in distraction prior to commencement of the study (Cohen, 2002; Cohen, Bernard et al., 2006; Cohen, MacLaren et al., 2006a) and in one of the studies, parents were also instructed in distraction (Cohen, MacLaren et al., 2006a). In all included studies, children were encouraged to engage in the distraction. There was moderate to very low quality evidence for the critical outcomes of distress due to imprecision +/- risk of bias. The results were mixed; there was evidence of a benefit for pre-procedural distress [(n=216); SMD -0.49 (95% CI -0.76, -0.22)] and distress acute and recovery combined [(n=126); SMD -0.68 (95% CI -1.04, -0.32)]. In the analysis including the largest number of studies (n=456), there was no evidence of a benefit for acute distress: SMD -0.63 (95% CI -1.53, 0.27)."* (HELPinKIDS 2.0 CPG Recommendation 32).[3]

Video: For Children >3-12 years

Evidence: "*Five studies including children aged 2 to 12 years were included in the systematic review (Cassidy et al., 2002; Cohen et al., 1997; Cohen et al., 1999; Cohen et al., 2015; Luthy et al., 2013). Nurse immunizers, parents and/or children received verbal, written or video instruction in distraction in 2 of the studies (Cohen et al., 1997, Cohen et al., 1999) and children typically watched a cartoon or movie on a television. There was very low quality evidence for critical outcomes (pain and fear) due to risk of bias and imprecision. There is no evidence of a benefit for pain or fear. When the single study that allowed the child to choose from several available videos (Cohen et al., 1997) was examined separately, a benefit of video distraction was observed for pain. There was very low quality of evidence for distress (important outcome) and evidence of a benefit across all 3 indicators assessed. In the analysis including all 5 studies (n=327), the SMD was -0.96 (95% CI -1.85, -0.08)."* (HELPinKIDS 2.0 CPG Recommendation 36).[3]

Verbal Distraction: For Children >3-12 years

Evidence: *"Two studies on parental verbal distraction including 46 children aged 3 to 7 years were included in the systematic review (Gonzalez et al., 1993; O'Laughlin & Ridley-Johnson, 1995). Parents were instructed either by using a pamphlet, or by oral instruction plus listening to a tape and practicing. Parents then distracted their child by talking to them, counting, singing, discussing other objects in the room, reciting a poem/rhyme, or other. There were no studies that examined verbal distraction provided by a clinician. There was low quality evidence due to risk of bias and imprecision for one of the critical outcomes (pain) and no evidence for the other (fear). There was no evidence of a benefit on pain. Given the young age range of the participants and that self-report may have been challenging (Chambers & Johnston, 2002; von Baeyer, Forsyth et al., 2009), we also examined*

distress; there was low quality of evidence for distress (important outcome) and evidence of a benefit for the analysis that included both studies: SMD -1.22 (95% CI -1.87, -0.58).” (HELPinKIDS 2.0 CPG Recommendation 35).[3]

Visual Distraction: For Adults

Evidence: **“***No studies were identified specific to vaccine injections. Two studies including adults undergoing venipuncture were included in the systematic review (Cason & Grissom, 1997; Jacobson, 2006). A kaleidoscope was used as the distractor in both studies. There was very low quality evidence for critical outcomes (pain, fear) due to risk of bias, indirectness and imprecision and no evidence of a benefit for both critical outcomes.”* (HELPinKIDS 2.0 CPG Recommendation 40).[3]

Breathing interventions

“*Breathing interventions have been proposed to reduce pain and fear during medical procedures. A variety of techniques have been studied, including; deep breathing or blowing, coughing, forceful breath-holding or exhalation. Breathing facilitated with toy distractors typically includes bubbles or pinwheels. Deep breathing (i.e., belly or diaphragmatic breathing) which causes body relaxation, is often included in cognitive-behavioural treatments for pain (Benson, 1975; Schaffer & Yucha, 2004; Uman et al., 2013); however, it is unclear to what degree it was incorporated in the reviewed studies.”* (HELPinKIDS 2.0 CPG).[3]

Breathing with a toy distraction (e.g., blowing bubbles, pinwheels): For Children >3-12 years

Evidence: **“***Six studies including 368 children aged 3 to 9 years were included in the systematic review (Beran et al., 2013; Blount et al., 1992; Bowen & Dammeyer, 1999; Krauss, 1997; Manimala et al., 2000; Sparks, 2001). In three of them, parents and children received instruction prior to the procedure. A variety of props were used to facilitate breathing, including: bubbles, pinwheels, and responding to a robot’s request to blow dust off a toy. There was very low quality evidence for critical outcomes (pain, fear) due to risk of bias and imprecision. There was evidence of a benefit for pain [n=123; SMD -0.49 (95% CI -0.85, -0.13)]. There was no evidence of a benefit for fear. There was very low quality of evidence for distress (important outcome). In the analysis including the largest number of studies (n=222 participants), there was evidence of a benefit for pre-procedure, acute and recovery distress combined: SMD -0.55 (95% CI -0.82, -0.28).***”*** (HELPinKIDS 2.0 CPG Recommendation 41).[3]

Breathing without a toy distraction (deep breathing, blowing): For Children >3-12 years

Evidence: **“***Two studies including 136 children aged 3 to 7 years were included in the systematic review (Cohen et al., 2002; French et al., 1994). In both studies, children were instructed in breathing exercises prior to vaccinations. In one study (Cohen et al., 2002), children watched a video introducing “snake breathing” where they are instructed to breathe deeply with a hissing sound. Introducing breathing in this way may have helped to make the strategy more concrete/clear and interesting; however, it was also potentially fear-inducing. The video also taught children about positive self-statements (i.e., “I am cool and calm”) and showed a child modelling these strategies. In the second study (French et al., 1994), children were instructed to take a deep breath and blow and blow and blow until they were told to stop. There was very low quality evidence for critical outcomes (pain and fear) due to risk of bias and imprecision and no evidence of a benefit. There was very low*

quality of evidence for distress (important outcome) and no evidence of a benefit." (HELPinKIDS 2.0 CPG Recommendation 42).[3]

Breathing Interventions (cough): Children >3-17 years

Evidence: "One study including 136 children 4 to 13 years was included in the systematic review (Wallace et al., 2010). Children were asked to cough during vaccination. There was low quality evidence due to risk of bias and imprecision. There was no evidence of a benefit on pain, one of the critical outcomes and no data for fear, the other critical outcome." (HELPinKIDS 2.0 CPG Recommendation 43).[3]

Breathing Interventions (cough, breath-hold): Adults

Evidence: **"***No studies were identified specific to vaccine injections. Two studies including 138 adults undergoing venipuncture were included in the systematic review (Basaranaglu 2006, Usichenko 2004). In one study, participants coughed during the procedure. In the other, participants were asked to perform a deep inspiration and then breath-hold. There was very low quality evidence for the critical outcome of pain due to risk of bias, indirectness and imprecision. There was evidence of a benefit for pain: SMD -0.82 (95% CI -1.21, -0.43). There was no evidence for the critical outcome of fear.*" (HELPinKIDS 2.0 CPG Recommendation 44).[3]

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: There is some evidence of benefit of different distractors in different ages: toys and videos in young children 0-3 years; music, videos, verbal distraction, and toys with breathing in children >3-12 years; and breathing interventions in adults. Some individuals may prefer to attend to the procedure as that is their style for coping and this should be taken into consideration when using distraction (as per below under acceptability).

Resource use and value for money: Distraction requires tools such as music players, video screens and toys which may not be procurable in LMIC. Breathing interventions evaluated for adults require no additional tools.

Impacts on equity: There are potential inequities for music, videos, breathing with a toy if some are able to access this intervention while others are not. There is no inequity with use of breathing interventions for adults.

Acceptability: Child and adult characteristics need to be considered: The effectiveness of distraction depends on intrapersonal and interpersonal variables and the attributes of the distractor. For example, distraction may be less effective or even may have counterproductive effects in individuals who perceive pain as highly threatening (i.e., have high levels of catastrophizing or worrisome thoughts about pain.[28,29,30] Breathing interventions are expected to be acceptable for adults.

Feasibility (implementability): Music may be the most feasible distraction as it is the most accessible globally. Although no studies have been conducted on the effectiveness of singing it is likely to work. Other distractions such as videos and toys may be possible depending on context. The results of distraction interventions are highly variable (as described above) and there are concerns about

fidelity of the intervention. For adults, breathing interventions are feasible although minor teaching may be required, which can be accomplished during the vaccination episode.

Other: Many distraction techniques have limited evidence and variable effectiveness. In children, youth, and adults, the universally effective intervention is topical anaesthetics. If topical anaesthetics are not affordable or accessible, we need to optimize the distraction intervention.

10. Oral analgesics

"*Acetaminophen and ibuprofen are analgesics commonly administered in children and adults to treat fever and pain. They have been used in the context of vaccination in order to prevent and abort vaccine-induced fever and 'delayed' pain (i.e., occurring hours to days after vaccination) (Manley & Taddio, 2007). There is some controversy regarding their routine use to prevent and/or treat side effects of vaccination because of the potential to interfere with the immune response of some vaccines (Prymula et al., 2009). For the purposes of this guideline, a summary of the research evidence regarding the effectiveness of acetaminophen and ibuprofen specifically for reducing acute pain (rather than delayed pain) during vaccine injections was reviewed*." (HELPinKIDS 2.0 CPG).[3]

Evidence: *"No studies specific to mitigation* of pain at *vaccine injections were identified. One study including children aged 1 to 18 years with cancer undergoing needle insertion into a subcutaneously implanted port was included in the systematic review (Hedén et al., 2014). Children received either acetaminophen (40mg/kg) or placebo 1 hour prior to port access. There is low quality evidence for pain (critical outcome) due to indirectness and imprecision and no evidence of a benefit from this intervention.*

Five studies were identified that examined the potential for interference with the immune response with acetaminophen use prior to vaccination. Three studies including 442 adults receiving influenza vaccine demonstrated no difference in the immune response for those who received acetaminophen compared to placebo (Aoki et al., 1993; Chernesky et al., 1993; Gross et al., 1994). In one study including 496 health care workers receiving hepatitis B vaccination series, a 26% reduction in hepatitis surface antigen antibodies was observed in the acetaminophen group (Doédee et al., 2014). Similarly, in one longitudinal study including 459 healthy infants following their primary and booster vaccination (10-valent pneumococcal non-typeable Haemophilus influenza protein D-conjugate vaccine, diphtheria-tetanus-3-component acellular pertussis-hepatitis B-inactivated poliovirus types 1, 2, and 3-H influenzae type b vaccine and rotavirus vaccine), lower levels for all 10 pneumococcal vaccine serotypes, protein D, anti-diphtheria, anti-tetanus and anti-pertactin was observed in the prophylactic acetaminophen group (Prymula et al.,2009). The proposed mechanism for reduced immunogenicity is interference with the early interactions of the dendritic cells, T cells and B cells of the primary immune response to conjugate and toxoid vaccines via reduction of inflammatory signals at the injection site (Prymula et al., 2009)." (HELPinKIDS 2.0 CPG Recommendation 20).[3]

With regard to ibuprofen, *"No studies specific to vaccine injections were identified. One crossover trial including 10 adult volunteers undergoing venipuncture was included in the systematic review (Smith et al., 1996). Adults received ibuprofen 5% cream and lidocaine-prilocaine 5% cream 1 hour prior to venipuncture. There is very low quality evidence for pain (critical outcome) due to indirectness (procedure, route of administration of ibuprofen, and active comparison group) and imprecision. Pain scores were higher for the ibuprofen group compared to lidocaine-prilocaine 5%.*

No studies were identified that evaluated the effect of ibuprofen on vaccination antibody response. Ibuprofen is an inhibitor of the cyclooxgenase enzyme and it is unclear whether blocking the metabolites of this enzyme system will interfere with vaccine effectiveness (Chen et al., 2009)." (HELPinKIDS 2.0 CPG Recommendation 21).[3]

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and Harms: Due to the lack of evidence of clear benefits and the potential for harms in terms of reducing efficacy of vaccines, oral analgesics were not recommended by the technical consultation group for pain mitigation at the time of injection. Oral analgesics can still be used in an individual context to mitigate the fever and local pain that may be experienced post vaccination.

Other interventions reviewed and not recommended for global use *and included in HELPinKIDS 2.0 CPG Recommendation* - See Appendix 2

- Non-nutritive sucking
- Simultaneous injections
- Manual tactile stimulation
- Warming the vaccine
- Vapocoolants

Other interventions for which the evidence is NOT presented in this document but included in HELPinKIDS 2.0 CPG[3]

- Muscle to be injected
- Muscle tension to decrease fainting
- Tactile stimulation using vibration and cold
- Skin to skin contact in neonates
- Strategies to address individuals with high levels of needle fear

Education of clinicians, children, adults and caregivers

Evidence presented during the consultation and *Evidence to Decision Elements of GRADE_DECIDE framework* are provided in **Appendix 3** as it was agreed that these should not be seen as separate interventions but part of the implementation process for recommended interventions.

Interventions for which there is no evidence

The technical consultation group considered a number of interventions for which there is no evidence for reducing pain or distress, including:

- effects of changing the needle after drawing the vaccination solution;
- effects of looking at versus away from the needle during injection; and
- effects of the setting in which vaccination occurs, such as whether being immunized in private or with many people has an effect on pain.

Due to a lack of evidence, these interventions are not currently recommended. Of note changing the needle could not be an alternative in the context of WHO's policy on the exclusive of auto-disable syringes for immunization as the specification for those syringes include the fact that the needle cannot be detached from the syringe.

Consultation with industry

Efforts were made to solicit industry's input through both the International Federation of Pharmaceutical Manufacturers & Associations and the Developing Countries Vaccine Manufacturers Network. During the technical consultation, a representative from a vaccine manufacturing company was invited to share information about ongoing efforts/initiatives the vaccine industry is undertaking/pursuing to address the issue of acute pain during vaccination. The representative informed the group of the following:

- Manufacturers evaluate the safety and tolerability of the vaccines licensed or in development assessing local reactions including pain as requires by the regulatory agencies, but they do not specifically evaluate pain at time of injection
- No known manufacturers are systematically collecting data on pain during injection
- Manufacturers recognize that pain correlates with vaccination schedules (e.g. multiple injections), and understand that pain and fear of injections influence vaccine hesitancy
- There are no known current activities/ongoing initiatives on reducing pain during vaccination

Group members posed the following questions to the industry representative:

- Could pain at the time of vaccination be measured as part of vaccine development (e.g. chemicals chosen, pH, isotonicity)? This is important since one of our recommendations is to inject the most painful vaccine last, and in order to do so we need an objective method of rating the painfulness of different vaccines.
- Could pain at the time of vaccination be included as an endpoint during formulation and early trials, and captured on case report forms? Could manufacturers be made obligated to collect this data if regulatory bodies made it a licensing requirement and the pain at time of vaccination profile be included in the package insert?
- Could advice be included in package insert to vaccine administrators on how to reduce pain, which would have to go through the regulators?
- Could different manufacturers be incentivized to collaborate to develop less painful vaccines and combination vaccines?

Consultation with National Immunization Managers in Africa (implementability survey)

Participants: Twenty-five managers from 25 different African countries participated in an implementability of intervention survey. These surveys took place at two sub-regional African Immunization managers meetings, one Francophone and one Anglophone.

Methods: Each participant was provided with questions and four exemplar recommendations [1. Do NOT aspirate when giving vaccines to all ages (strong recommendation), 2. Administer vaccines from the least to the most painful vaccine for all ages (strong recommendation), 3. Breastfeed at time of immunizations for infants (conditional recommendation: for women who are breastfeeding and for whom breastfeeding during the vaccination session is culturally acceptable in the vaccination setting), 4. Use neutral words at the time of vaccination; avoid language that increases anxiety (strong recommendation) for all ages as examples and asked to respond to a written survey on a series of evidence to decision implementation questions. The responses are summarized below in connection with the questions asked and the complete responses appear in **Appendix 4**.

1. Are there cultural or gender dimensions that might impact on the implementation of these recommendations? Responses: No issues reported by majority of participants, but sometimes breastfeeding identified as a potential issue

2. How might the patient's values and preferences impact the implementation of these recommendations? Response: Parents most concerned about pain, and post vaccination pain where they may want medications, but influenced by knowledge, attitudes and previous experience of vaccinations. Recommendations predicted to be positively viewed by parents and could lead to higher acceptance of vaccines.

3. How feasible will it be to train health care workers and implement these recommendations? Response: Feasible commonly reported, suggestions for Train of trainers, but Ministry of Health training needs updates, need formative training and supervision, need theory and practical training.

4. What do you see as some of the main barriers from the health care worker perspective? Response: Poor knowledge and noncompliance of workers- training needed, stopping aspiration, long history of neglecting pain, some workers mirror the child's reaction- i.e. crying with child so this will may be difficult to change.

5. Do you believe health care workers will accept these new recommendations? Response: Most commonly reported as acceptable, but may need to convince workers that pain is unacceptable, you need to explain and follow-up.

6. What recommendations are most likely not to be followed early on? Response: Variable- dependent on what recommendations already being done in practice and training- see Appendix 4.

7. What recommendations do you feel are most likely to be followed early on? Response: Variable- depending on what is already being done in practice and training- see Appendix 4.

8. What do you feel will be the cost of the time, training, and implementation of these recommendations? Response: Minimal cost commonly reported, best to integrate with existing training and training for new vaccines: plan cascade of training from national to district levels.

Conclusions: There was consistency among the 25 African immunization managers: culture and gender were not concerns, with the rare exception of certain women who may be reluctant to breastfeed in a public clinic. Parents are concerned about pain and so these proactive recommendations will be well received and may improve acceptance of vaccine. The new recommendations are feasible but training will be needed. Main obstacles centred on previous

practice (aspiration), conducive conditions for breastfeeding, training workers to understand and value pain prevention recommendation. Virtually all predicted acceptability for recommendations, but there was some variation, depending on local practice, as to which recommendations would be most easily implemented.

Limitations and additional notes

- The evidence on the effectiveness and safety of interventions, while coming from all regions (see Figure 1), predominately came from the region of the Americas and the European region and from High Income Countries.
- The evidence was limited to what had been included in HELPinKIDS 2.0 CPG.
- The HELPinKIDS 2.0 CPG used a strict approach in using GRADE that often resulted in reporting high levels of uncertainty of evidence.
- The evidence base for many interventions did not cover all the age groups of interest thus requiring extrapolation for recommendations. Attention to WHO age categorization and related immunization programs will be important in the future.
- Psychological interventions maybe very operator dependent as well as having inter-subject variability e.g. distraction.
- Trials that examined multiple pain mitigation strategies being used at the same time were not included; in many cases, however, co-interventions could have occurred: e.g. breastfeeding at same time as most painful injected last. Combining effective interventions may improve pain relief beyond individual interventions.
- Many of the trials were done in clinical settings that are not reflective of the range of environmental conditions in LMIC.
- Complex psychological interventions such as hypnosis were excluded as impractical.
- Intramuscular versus subcutaneous administration for vaccines was not assessed due to the scantly evidence base and the potential to make recommendations that may disagree with the manufacturer's approved route.
- Complementary and alternative medicine was excluded.
- Given that pain in general is not well addressed in low resource settings[31] there is a need to draw attention to pain mitigation at the time of vaccination. This may increase awareness about pain in other contexts and improve the quality of care delivered across the health care continuum.

Future research questions

The group identified gaps in the literature that would be useful for informing future recommendations on reducing pain during vaccination. The following questions were prioritized from a larger list for research from a global perspective:

- Is there a difference in pain on injection between delivering intramuscularly or subcutaneously for vaccines that are licensed for administration by either route e.g. measles-containing vaccines?

- What distractions, in the ages where applicable, are effective and implementable?
    - Which distractions are appropriate in different geographical contexts and income settings?
    - How should distractions be administered?
- Is there any difference in pain on injection when using multiple injections in one limb or multiple limbs?
- What interventions to reduce pain during vaccination are effective in mass campaigns and school-based programs?
    - What environmental interventions are effective (e.g. privacy, visual cues)?
- Other research questions not prioritized:
    - Can additional head-to-head studies and add-on studies be conducted to determine the relative effectiveness of different interventions and the additive effects of interventions?
    - Can additional studies be conducted to determine how parents and individuals undergoing vaccination in different contexts want to learn about preventing pain at the time of vaccination? This will help identify proper health promotion avenues that could help strengthen other health care messages as well.

Conclusions

Pain and distress at the time of vaccination is an important clinical issue for individuals of all ages undergoing vaccination, their caregivers and health care providers administering vaccinations. Not addressing pain at the time of vaccination can engender vaccine hesitancy and may impact on future heath seeking behaviour and health care decisions. There are evidence based strategies to mitigate pain at the time of vaccination that are feasible, culturally acceptable and can be applied in high, middle and low income countries. Addressing pain and distress at the time of vaccination is especially important for young and school-age children who are at highest risk of the adverse sequelae of untreated pain (i.e., development of needle fears and long-term negative attitudes and non-compliant behaviours). For infants, young and school aged children, a more comprehensive approach is recommended due to the high levels of distress associated with vaccine injections and potential for long-term harm of unmitigated pain. When sufficiently mature and able to give their preferences, a more self-directed and individualized approach can be used. As the relief of pain during health-related procedures is also accepted as a basic human right, mitigation of pain at vaccination should be part of good vaccination practice around the globe.

Recommendations and implementation

Interventions for reducing pain, distress and fear at the time of vaccination

The following are interventions (recommended and not recommended) for reducing pain, distress and fear during vaccination, categorized by age:

All ages	
Recommended for national programmes	**Not recommended for national programmes as routine practice**
• **No aspiration** • **Administer vaccines in order of increasing painfulness** • **Proper positioning** • **Use of neutral words; avoiding language that increases anxiety and/or promotes distrust**	Effective but not practical* • Topical anaesthetic Unknown effectiveness: • Changing the needle • Looking at vs. away from needle • Organizational aspects of the setting: privacy, environment Ineffective: • Manual stimulation Ineffective with potential harms: • Oral analgesics • Warming the vaccine

Infants	
Recommended for national programmes	**Not recommended for national programmes as routine practice**
• **Caregiver presence** Conditional recommendations: • **Breastfeeding** • **Administration of sweet solutions** if breastfeeding not acceptable during the vaccination session or shortly before (including rotavirus vaccine)	Effective but not practical: • Pacifiers and finger/thumb sucking • Simultaneous injections Equivocal effectiveness and impractical • Distraction Ineffective: • Vapocoolants

Children	
Recommended for national programmes	**Not recommended for national programmes as routine practice**
• **Caregiver presence** Conditional recommendations: • Distraction (e.g. Music)	Ineffective: • Vapocoolants

Adolescents and Adults (including pregnant and breastfeeding women)	
Recommended for national programmes	**Not recommended for national programmes as routine practice**
Conditional recommendations: • Distraction (no evidence that effective in adolescents) ○ Breathing interventions (cough, breath-hold)	Equivocal effectiveness and not practical: • Vapocoolants (no evidence that effective in adolescents) Ineffective: • Visual distraction • Music distraction

*practicality encompasses cost, feasibility and acceptability

Recommendations to WHO

The technical consultation group recommends the following to WHO in consideration of implementation of the above interventions:

- Ensure alignment of guidance documents or statements posted on the web with the above mentioned recommendations.
- Include pain mitigation recommendations within WHO immunization materials.
- Align pain mitigation recommendations with other departments and policies[2] e.g. breastfeeding, pacifiers, rotavirus vaccine, aspiration, etc.
- Disseminate pain/fear mitigation recommendations through SAGE report and its usual dissemination channels, Expanded Programme on Immunization (EPI) managers, National Immunization Technical Advisory Group (NITAG) members and partners.
- Consider publication of a specific self-standing guidance document or inclusion with other immunization practice guidance.
- Complete the training modules for mid-level immunization managers (MLM) with respect to interventions to reduce pain at the time of the vaccination event.
- Monitor and evaluate implementation success of pain mitigation measures.
- Encourage/promote generation of data on immediate pain at the time of vaccination during vaccine development and Adverse Event Following Immunization (AEFI) reporting.[4]
- Work with the Expert Committee on Biological Standardization (ECBS) and regulatory agencies to advocate that grading of pain experienced during the vaccination event be included in data for licensing and in the product monograph.

Recommendations to countries

The technical consultation group recommends the following to countries in consideration of implementation of the above interventions:

- At the health system level:
  - Strengthen health policy by:
    - Including the mitigation of vaccination pain and fear at the time of injection as part of good vaccination practice, and
    - Recognizing pain and fear at the time of injection as distinct from other pain adverse events and as one factor in selection of a vaccine.
  - Support and monitor implementation success (ICC/NITAG).

- Integrate recommendations into immunization programs by:
    - Providing preferred order of injection for country-specific vaccination schedules
  - Include vaccine pain mitigation in health care worker curriculae.
- Through education of health care workers and pre-service workers, and continuing education:
  - Ensure understanding and appreciation of pain and fear with vaccination injection.
  - Include the following content:
    - Assessment of pain and fear during the time of vaccination; and
    - Mitigation of pain and fear at the time of vaccination, including interventions such as
      - No aspiration,
      - Using the most painful injection last,
      - Positioning,
      - Language and interaction, and
      - Other interventions tailored to age-specific groups such as breast feeding for infants.
- Through education of caregivers, and those receiving vaccines who are old enough to be educated (adults, older children, youth) :
  - Include education on vaccination pain mitigation:
    - during pre-natal visits,
    - with breastfeeding education, and
    - at the time of vaccination.
  - Methods of education could include pamphlets, one-on-one or group verbal instruction, posters, and other techniques.

Appendix 1: Declaration of Interests

All eight experts participating in the 16-17 February 2015 Technical Consultation completed a declaration of interests. Two experts reported relevant interests that are summarized below. All interests were assessed not to constitute a conflict of interest in regard to serving on the Technical Consultation. It was concluded that all members could take part in full in all of the discussions.

Professor Anna Taddio

- Received an investigator-initiated grant from Pfizer (2011-2015) for a longitudinal randomized controlled trial investigating the effectiveness of parent-led interventions in reducing infant hypersensitivity to pain. This interest was assessed as non-personal, specific and financially significant.*
- Received supplies from Natus[32] and Ferndale[33] in relation to research on reducing vaccine injection pain. These interests were assessed as non-personal, specific and financially significant.*

Professor Christine Chambers

- Provides occasional consulting to AbbVie[34] on topics such as pain management and needle fears in persons living with inflammatory bowel disease. This interest was assessed as personal, specific and financially significant.*

* According to WHO's Guidelines for Declaration of Interests (WHO expert), an interest is considered "personal" if it generates financial or non-financial gain to the expert, such as consulting income or a patent. "Specificity" states whether the declared interest is a subject matter of the meeting or work to be undertaken. An interest has "financial significance" if the honoraria, consultancy fee or other received funding, including those received by expert's organization, from any single vaccine manufacturer or other vaccine-related company exceeds 5,000 USD in a calendar year. Likewise, a shareholding in any one vaccine manufacturer or other vaccine-related company in excess of 1,000 USD would also constitute a “significant shareholding”.

Appendix 2: Other HELPinKIDS 2.0 CPG Recommendation interventions reviewed and not recommended for global use

1. Non-nutritive sucking

"Non-nutritive sucking is defined as sucking not relating to or providing nutrition and is recognized for its pacifying effects in infants (Jenik & Vain, 2009). Non-nutritive sucking can be achieved using a variety of methods, including finger/thumb or an external device (pacifier/soother). Non-nutritive sucking has been the subject of much research and controversy regarding its potential effects, both negative and positive (reviewed in Nelson 2012). For the purposes of this guideline, a summary of the research evidence regarding its effectiveness specifically for reducing distress during vaccine injections was reviewed. The mechanism of action of non-nutritive sucking in this context, while not known, has been hypothesized to involve the activation of orotactile and mechanoreceptors, which may inhibit nociception or provide distraction (McNair et al., 2013). There is evidence for the efficacy of non-nutritive sucking for procedural pain management in neonates (Pillai Riddell et al., 2011)." (HELPinKIDS 2.0 CPG).[3]

Evidence: *"Two studies including infants from 0-4 months of age were included in the systematic review (Liaw et al., 2011; Taavoni et al., 2010a). There was low to very low quality of evidence across the different outcomes of distress (critical outcome) due to risk of bias and imprecision and evidence of a benefit of the intervention. In the only analysis that contains data from both studies (n=186), the SMD was -1.88 (-2.57, -1.18) for acute distress. The rate of sucking may be important for effectiveness; included studies did not determine sucking rate."* (HELPinKIDS 2.0 CPG Recommendation 12).[3]

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: There is evidence of benefit with non-nutritive sucking. However, finger/thumb sucking may not occur spontaneously at the time needed. WHO advises against the use of pacifiers for breastfeeding infants.[35]

Resource use and value for money: For infants that suck their own thumbs or that use a pacifier, no additional resources are needed. It is unlikely that health care facilities would supply pacifiers for the sole purpose of mitigating vaccination pain. An adult may be required to hold the pacifier in place to stimulate sucking and prevent the device from falling out of the infant's mouth.

Impacts on equity: This intervention with a pacifier may be inequitable if some have access to pacifiers and others do not.

Acceptability: Pacifiers are not available or used globally. Sucking on finger/thumb is acceptable in young infants but may not occur at time needed.

Feasibility (implementability): It is not feasible for infants who do not regularly use pacifiers to begin solely for the purpose of reducing pain during vaccination and finger/thumb sucking does not always occur spontaneously at the moment needed.

Other: None

2. Simultaneous injections

"At present, immunization schedules commonly recommend more than one separate vaccine injection at a single visit. There is the possibility to inject multiple vaccines simultaneously rather than sequentially. On the one hand, rapid administration of both injections at once may help reduce pain due to sensitization (i.e., increase in pain intensity over time due to repeated nociceptive stimulation) and less anticipatory distress. In contrast, some children might find it alarming to be approached by more than one individual with a needle at once. The potential for differences in how this intervention might work across childhood due to differences in the factors described above led us to examine the effects of this intervention for infants and children separately." (HELPinKIDS 2.0 CPG).[3]

Simultaneous injection: In Infants (<1 yr)

Evidence: "*Two studies including infants aged 2 to 6 months were included in the systematic review (Hanson et al., 2010; McGowan et al., 2013). There was low quality evidence for distress (critical outcome) due to risk of bias and imprecision. The results were mixed for different indicators of distress. In the only analysis that included data from both studies (n=172), acute distress was lower in the infants in the simultaneous injection group: SMD -0.56 (-0.87, -0.25). There were no identified undesirable consequences to the infant although this has not been well studied.*"(HELPinKIDS 2.0 CPG Recommendation 3).[3]

Simultaneous Injection: In children 1- 10 years

Evidence: "*One study including children aged 4 to 6 years was included in the systematic review (Horn et al., 1999). There was very low quality evidence for pain (critical outcome), primarily due to high risk of bias (lack of blinding and standardization of procedures, imbalance in baseline characteristics of study groups) and low sample size (n=44 included in analysis). There was no evidence of a benefit of this intervention. Having two clinicians present to administer vaccine injections simultaneously may increase child fear. There may also be alterations in positioning of children and restraining of children to ensure that simultaneous injections can be administered safely, which can further increase fear."* (HELPinKIDS 2.0 CPG Recommendation 4).[3]

Conclusions

Though there is evidence of benefit for this intervention in infants but not in children, consistent availability of multiple immunizers was not considered feasible in many high, middle or low-income settings. Therefore, this intervention was considered effective in infants but not practical and was not discussed in detail.

3. Manual tactile stimulation

"*Stimulation of the skin (tactile stimulation) adjacent to the site of a simultaneously occurring painful medical procedure or on the contralateral side by manually rubbing, stroking or applying pressure or applying a vibrating device has been evaluated to reduce pain from needle procedures. The proposed mechanism of action involves the gate control theory of pain and the notion that the touch sensation competes with the pain sensation to reduce the pain signal to the brain (Wall 1978)."* (HELPinKIDS 2.0 CPG).[3]

Evidence: *" Six studies including individuals from infancy until adulthood were included in the systematic review (Chung et al., 2002; Hogan, Probst et al., 2014; Jose & Shetty, 2012; Nakashima et al., 2013; Sparks, 2001; Taddio, Ho et al., 2014a). There was moderate to very low quality evidence for critical outcomes (pain and distress), in part due to high risk of bias, inconsistency and imprecision. There was no evidence of a benefit for pain (n=893): SMD -0.38 (95% CI -0.96, 0.21). Similarly, there was no evidence of a benefit for any indicator of distress. In the analysis of acute distress that included all the relevant studies (n=301 participants), the SMD -0.69 (-1.77, 0.39). The evidence base includes heterogeneity in the delivery of the intervention, type of injection, and co-interventions. Aspects of the intervention and the process of administering vaccines used in the trials (e.g., pinching the skin or securing the limb) may have introduced contamination that offset the benefit of this intervention."* (HELPinKIDS 2.0 CPG Recommendation 13).[3]

Conclusions

As there is evidence that this intervention is ineffective, a recommendation against manual stimulation was made by the technical consultation group.

4. Warming the vaccine

"*Injectable medications which deviate from normal body temperature in either direction may activate nociceptors, leading to the sensation of pain. Altering the temperature of medications has therefore been undertaken to try to counter the potential pain-inducing effects. With respect to vaccines, they are usually refrigerated and their cold temperature may contribute to the pain experienced by individuals during administration."* (HELPinKIDS 2.0 CPG).[3]

Evidence: *"One study including 150 adults was included in the systematic review whereby vaccines were warmed (either by rubbing or by an incubator) immediately prior to injection (Maiden et al., 2003). There was low level quality of evidence for the outcome of pain (critically important outcome) due to risk of bias and imprecision and no evidence of a benefit of warming the vaccine. Of note, the temperature achieved in the intervention group was below body temperature (by approximately 10 degrees centigrade). Temperatures that are closer to body temperature may be required to have an observable impact on pain, as suggested by a previous systematic review of warming local anaesthetics prior to injection which showed that warming to body temperature effectively reduced infiltration pain (Hogan et al., 2011). It is also important to consider the effect of warming vaccines on their biologic activity. Correct storage and handling of vaccines is of paramount importance to their effectiveness."* (HELPinKIDS 2.0 CPG Recommendation 15).[3]

Conclusions

As there no evidence for effectiveness of this intervention and potential for harm if the vaccine is warmed for a duration or to a temperature as to render its components inactive, warming the vaccine was recommended against by the technical consultation group.

5. Vapocoolants

"*Vapocoolants are volatile liquids applied on the skin right before the procedure that immediately reduce the temperature of the surface of the skin as they evaporate, resulting in a sensation of cold*

at the application site (Hogan, Smart et al., 2014). Vapocoolants may reduce pain by competing with the pain sensation or decreasing the velocity of neural impulse conduction (Hogan, Smart et al., 2014). In some individuals, however, the sensation of cold is itself painful and increases attention on the impending pain of injection. The effectiveness of vapocoolants was examined for 3 different age groups separately (i.e., infants, children, and adults) due to the potential for differences in how the intervention may be perceived across ages." (HELPinKIDS 2.0 CPG).[3]

Vapocoolants: Children up to 3 years

Evidence: *"One study was included in the systematic review including 60 infants aged 2 to 6 months of age (Maikler 1991). There was low quality evidence for the outcome of distress (critical outcome) due to risk of bias and imprecision, and no evidence of a benefit."* (HELPinKIDS 2.0 CPG Recommendation 26).[3]

Vapocoolants: Age >3-17 years

Evidence: *"Five studies including 268 children aged 2 to 12 years were included (Abbott & Fowler-Kerry, 1995; Eland 1981; Cohen et al., 2009; Cohen Reis & Holubkov, 1997; Luthy et al., 2013). Vapocoolants were administered using various techniques (e.g., direct spray, application of a cotton ball sprayed with vapocoolant). There was low quality evidence for pain (critical outcome) due to risk of bias from inconsistent or lack of blinding and imprecision and there was no evidence of a benefit. The results are consistent with the results of a recent systematic review of vapocoolants for venipuncture pain that demonstrated no evidence of a benefit for children up to 18 years (Hogan, Smart et al., 2014). Some children may find application of vapocoolants uncomfortable, which can augment their pain experience. The cold sensation can focus attention on the procedure, further augmenting pain.*" (HELPinKIDS 2.0 CPG Recommendation 27).[3]

Vapocoolants: Adults

Evidence: *"One study including 185 adults was included in the systematic review (Mawhorter, 2004). There was low quality evidence for the outcome of pain (critical outcome) due to risk of bias and imprecision; mixed results were observed for this outcome when measured over different time epochs. For acute pain, the SMD was -0.78 (95% CI -1.08, -0.48). For pain during the recovery phase, the SMD was -0.10 (95% CI -0.39, 0.19)."* (HELPinKIDS 2.0 CPG Recommendation 28).[3]

Conclusions

Due to the lack of evidence of benefit for this intervention in children, the technical consultation group does not recommend the use of vapocoolants in this population. While vapocoolants may be of benefit in adults they are expensive (about $1/dose), benefit may be offset by discomfort from application (due to stinging sensation from cold) and the evidence for the effectiveness of other preparations such as topical anaesthetics is more robust.

Appendix 3: Education of clinicians, children, adults and caregivers

Education of Clinicians

Health care providers who routinely give immunizations need to be knowledgeable about evidence based approaches to pain mitigation at the time of immunization as *"individuals receiving vaccinations value efforts made by clinicians to minimize pain and fear as it demonstrates that clinicians are competent and that they care about them (Taddio, Ilersich et al. 2014)."*[3] Training of health care providers can support use of evidence based pain mitigation interventions. Caregivers and those receiving vaccine injections can also benefit from education about these strategies.

Evidence: *"One study involving 53 public health nurses delivering vaccinations to 459 children was included in the systematic review (Chan et al., 2013). Public health nurses in the intervention group were trained in a variety of evidence-based pain treatments using a multi-faceted approach: 2-hour in-person education session including a power-point presentation and practice scenarios delivered by a nursing manager, and online support. The control group did not receive this education. There was low quality evidence for critical outcomes (use of pain interventions) due to risk of bias. There was an increase in the use of pain interventions in the training group: SMD 0.66 (95% CI 0.47, 0.85) (N.B. better indicated by higher values)."* (HELPinKIDS 2.0 CPG Recommendation 45).[3]

Education caregivers and children

Evidence: *"Five studies were included in the systematic review that evaluated education of 589 parents of children less than 2 years of age prior to the day of vaccination (Bustos et al., 2008; Cramer-Berness 2005 a; Taddio, Parikh et al., 2015; Taddio, MacDonald et al., 2014; Taddio, Smart et al., 2014b). In included studies, parents were trained in a variety of evidence-based pain treatments using different techniques, including: verbal instruction, pamphlets, and videos. Training took place in the hospital during prenatal classes or after delivery of an infant, and at outpatient clinics. These methods are consistent with usual methods and settings of education of the public about immunization. There was moderate to low quality of evidence across different indicators for use of pain interventions (critical outcome) with mixed results. In the analysis that included the largest number of studies (n=300 participants), there was a benefit on use of pain interventions: RR 2.08 (95% CI 1.51, 2.86) (N.B. better indicated by higher values). The results were mixed for distress in the children. In the analysis that included the largest number of studies (n=350 participants), there was a benefit on acute distress: SMD -0.35 (95% CI -0.57, -0.13). There were no data for other critical outcomes (pain, fear) due to the inability of included children to provide self-report as a result of their young age."* (HELPinKIDS 2.0 CPG Recommendation 47).[3]

"Four studies evaluated education of parents of children up to 6 years of age on the day of vaccination (Cohen et al., 2015; Cramer-Berness, 2005a; Taddio, Parikh et al., 2015; Felt et al., 2000). In included studies, parents were trained in clinics using a variety of techniques, including: verbal instruction, pamphlets, computer or videos. There was low to very low quality of evidence due to risk of bias and imprecision for one of the critical outcomes (use of pain interventions) and evidence of a benefit for this outcome. In the analysis including the largest number of participants (n=239), there was a benefit for parent use of intervention: RR 2.42 (95% CI 1.47, 3.99) (N.B. better indicated by higher values). There was a benefit for child use of intervention in one study including 60 children (Cohen et al., 2015): SMD 1.93 (95% CI 1.31, 2.55). There was no evidence of a benefit for pain. The

results were mixed for measures of child distress. In the analysis including the largest number of children (n=422), there was no evidence of a benefit for acute distress: SMD 0.05 (95% CI -0.89, 0.99). There was no data for the other critical outcome (fear).” (HELPinKIDS 2.0 CPG Recommendation 48).[3]

Education of Individual

Evidence: “*One study involving 51 female children undergoing vaccination aged 11 to 12 years in a school setting was included in the systematic review (Klingman, 1985). Children in the intervention groups were provided with 10 minutes of detailed information about the infectious disease being vaccinated against, the vaccination procedure and cognitive coping techniques. Then they either practiced by imagining the vaccine injection or asked questions. There was very low quality of evidence for the critical outcome of fear due to risk of bias and imprecision. The effects were mixed; there was a benefit for pre-procedural fear [SMD -0.67, 95% CI -1.28, -0.07)] but not acute fear [SMD -0.63 (95% CI -1.62, 0.36)]. There was no data for the critical outcome of pain. In the included study, children were vaccinated in groups of 5 and there may have been some contamination between educated and non-educated groups.”* (HELPinKIDS 2.0 CPG Recommendation 49).[3]

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: There is moderate to very low evidence for increased use of evidence based pain mitigation strategies with education of healthcare workers and parents and hence benefit. There is no evidence of harm on pain experience. However, teaching people about pain may give them expectation for pain to be treated and just cause for being dissatisfied if not done so adequately. This makes the health care system more accountable for providing quality level of care. As with the HELPinKIDS 2.0 CPG review team, the WHO review team values the use of these pain and distress mitigation techniques by clinicians “*in order to fulfil their ethical obligation to reduce unnecessary suffering and to demonstrate competency regarding best practices for vaccine injections”*[3]

Resource use and value for money: For health care providers, the only additional resources required are to build this training into existing education and training programs. For adults, youth, older children and parents opportunistic education could occur at the time of vaccination is discussed such as while waiting to be immunized.

Impacts on equity: There are no anticipated impacts on health inequity.

Acceptability: No concerns were expressed regarding cultural acceptability.

Feasibility (implementability): Education interventions were seen as feasible for those giving vaccines (health care workers), those receiving vaccines (adults, youth, older children) and caregivers. Provision of practical educational resources such as pamphlets, posters, etc., for caregivers, adults and older children and youth could support this process.

Other: None

Appendix 4: Implementation survey participant responses table

Questions: Eight questions related to the categories outlined below- note: "Late" refers to which recommendations participants felt would have a late update and "Early" refers to which recommendations participate felt would have an early update.

Exemplar Recommendations:
1. Do NOT aspirate; 2. Administer vaccines from the least to the most painful; 3.Breastfeed at time of immunizations; 4. Use neutral words at the time of immunization; avoid language that increases anxiety

Country	Culture/gender	Preference/values	Feasibility	Barriers	Acceptability	Late	Early	Cost
Algeria	No issues	Communication, and with MOH support	Without problem	None	Challenge to accept for some	2	3,4	
Botswana	Breastfeeding is culturally encourage	Recs. will be welcome by pts	Yes, but MOH training updates	None	Yes	0	4	Add to EPI-MLM train.
Burkina Faso	For 3, leave the initiative to the mother, if not certain cultural concerns regarding exposing a breast	Knowledge, attitudes, previous experience with vaccines and epi context	Yes, a training with theory and practice with role playing	Noncompliance of workers, the number of vaccines and the service of vaccination, and customs of populations	You need to inform, explain and follow	1,3,4	2	3 days
Cabo Verde	No issues	Nothing	Yes	few barriers	yes	0	1,2,3,4	Some time and reduced costs
Comoros Islands	For some, breast feed not culturally accepted	Good to have regular parent feedback	Training of trainers and cascade training	Poor knowledge of workers	yes	1	2	1/yr train
Cote D'Ivoire	No issues	In general, patient doesn't decide	Yes, with sensitivity training	There are some habits that may need challenging and changing	yes	1	3	Non mentioned

Eritrea	No issues	Preferences for oral vaccines	yes	No aspiration a challenge	Except for Aspiration	1	4	min
Ethiopia	Breast feeding may have culture issues for some	Pts may prefer to start with most painful injection	No aspiration will be challenging	History of neglecting pain, attitudes will need to change	Yes, but need to convince them pain is unacceptable	4,2	1,3	2-3 orientations and link to other training
Ghana	No issues	Lead to higher patronage for vaccination	Very feasible	No barriers anticipated	Yes	0	1,2,3,4,	2 months for a cascade of training from national to district levels
Liberia	No issues	Increased acceptance which lead to good coverage	Very feasible	Most workers still use words that will anger the caregiver	Yes	3	1	Request proper planning/budgeting based on needs
Madagascar	No issues	Pain has importance to parents to 2,4 are important	Need formative supervision along with training	Workers need additional training- and to communicate	Yes, if trained	4	2	Include in training, monitor, beyond HSS needed
Malawi	No issues	None	Easy to do	# of injections could be a challenge	Yes	4	1,2,3	No extra cost, link to current content and HCW training
Mali	Yes	Experience of Uniject led to rumours of risk of sterilization/contra-ception	Yes	Minimum barriers	Yes	0	1	Training of 3 or 4 days will be necessaire and into the training cascade
Mauritania	No issues	No concerns	Yes feasible	#3 not easy to implement because the mothers are not always available during vaccination	Yes	1,4	1,2	Yes +++ training of workers, and agents of vaccination

Mauritius	No issues	There will be no impact	It's not worth training	If you don't aspirate you might give vaccine in blood vessel	No	none	none	Number 4 only one worth training
Mozambique	No issues	Good acceptability	Integrate for new vaccines this year	Worried mothers need to hold baby for vaccine so breastfeeding would interfere	Yes but with scepticism because aspiration contradict previous training	1,3	2,4	Cost bearable if integrate to new vaccine, but substantial if done alone
Namibia	No issues	Does not think patient preference have impact	Training of workers is continuous and dynamic	Explanation of reasons will reduce barriers	Yes	0	all	Needs time for sure, these recommendations are not too many to need a lot of time
Niger	No issues	No impact	Yes, why not	In principle, but not without getting used to and encouragement	Yes, but it will demand some time	3	1,2,4	Cost of adapting
R. Guinea	No issues	No elements	Yes	Need training, need directives for the new ones, need supervision	Yes	3	1,2,4	Little info on breastfeeding, little costs
Sierra Leone	No issues	Acceptance	Very feasible, communication must be emphasized	Barriers: order of injection from least to most painful may not be adhered to without proper	Yes, with appropriate training- especially communication	1	3	Moderate to high

				training				
Swaziland	None in Swaziland	No impact	Very feasible	Health worker fear inflicting pain with multiple injections	Yes they will accept them	none	all	Not much cost as these can be communicate in various forums and posters etc..
Tanzania	No issues or very minimal		Feasible if linked to new vaccine	Sometimes workers mirror the child pain when cry with them, but generally are positive	Yes	4	1	
Uganda	No issues	Parents more concerned about pain reaction after and want meds to help with this	No aspiration could be confusing given policy for adrenal injection	Yes, as long as evidence is provided	Yes with evidence	1	3	Minimal
Zambia	No issues identified	3 is more or less a Recommendation in Zambia, number 4 may have some impact	A separate training not feasible, best to align with introduction of new vaccine	Changing from traditional aspiration, and neutral words, and putting each child on a feed all potential barriers	Yes but it will take time	1	3	Separate training not feasible, link to other training, difficult to attach cost
Zimbabwe	No issues	With good program communication no problems anticipated	Quite feasible	Giving too many injects, workers don't like inflicting too much pain	Yes	none	Most in practice	Integrate into ongoing trainings an supportive supervision and may not incur any separate costs

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[32] Natus Medical Incorporated is a provider of medical devices, software and services for newborn care, neurology, sleep, hearing and balance. The product supplied for research can be found here: http://www.natus.com/index.cfm?page=products_1&crid=451.
[33] Ferndale Pharmaceuticals Ltd specialises in dermatological medical devices, pharmaceuticals and dermo-cosmetics. The product supplied for research can be found here: http://www.lmx4.co.uk/.
[34] AbbVie is a pharmaceutical company. It does not manufacture drugs relevant to this Technical Consultation.
[35] Nutrition: Exclusive breastfeeding [Internet]. Geneva: World Health Organization; 2015 [cited 2015 Mar 22]. Available from: http://www.who.int/nutrition/topics/exclusive_breastfeeding/en/.

Sustainable Access to Vaccines in Middle-Income Countries (MICs): A Shared Partner Strategy

Report of the WHO-Convened MIC Task Force

March 2015

Executive Summary

Over the past decade, access to vaccines in middle-income countries (MICs) has been much debated. This focus on MICs has been fuelled by the realization that the majority of poor people and vaccine-preventable deaths are now in MICs and by a concern that this group of countries may be missing out on opportunities to introduce new vaccines, with donors focused on low-income countries (LICs). In light of the increased international attention to this issue and at the request of SAGE, in June 2014 WHO convened a Middle-Income Country Task Force to develop a coordinated strategy and plan of action.

To gain additional clarity on the nature of the problem, the Task Force's re-assessed immunization performance in all MICs. This analysis revealed that the great majority of vaccine-preventable disease burden is currently concentrated in donor-supported MICs, and that this group is the main driver of the lag in immunization performance in MICs relative to LICs, including in the fraction of the birth cohort with access to new vaccines. The notion that MICs have fallen behind donor supported countries may thus not well capture the issues at stake.

A comprehensive look at MICs performance shows that MICs are far from attaining the GVAP targets. While forty MICs are well supported by Gavi, another sixty-three countries do not benefit from a unified international strategy. In these countries, vaccine-preventable disease burden and numbers of unvaccinated children are relatively low compared to the Gavi MICs, but substantial and unacceptable nonetheless. Many of these countries have strong systems and the potential to make rapid gains if key barriers are removed.

It is on this latter group, the non-Gavi countries, that the MIC Task Force has decided to focus its MIC Strategy, mainly on the grounds of complementarity and global equity. Given the dynamic donor landscape and the anticipated exit of countries from Gavi support in coming years, it is envisaged that the MIC Strategy will also eventually benefit Gavi-graduated countries. The strategy will focus on an initial period from 2016-2020 coinciding with the remaining years of the Decade of Vaccines. For a second period (2021-2025), the Task Force proposes to develop as necessary an adapted strategy accounting for changes in the immunization and development landscape.

The Task Force has undertaken a careful study of both the needs of non-Gavi MICs and the types of support currently provided to these countries by immunization partners. Based on this and on a modelled analysis of impact, the Task Force has agreed that its strategy should address both new vaccine introduction and immunization coverage. The proposed MIC Strategy focuses on four main areas: 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; iv) improving access to timely and affordable supply. Within each of these broad areas, the Task Force has identified a set of focus activities and lead agencies.

Each area of the strategy is important in its own right and will contribute to the overall objectives of raising and sustaining equitable immunization coverage and enabling introduction of new vaccines. But the Task Force also believes that the elements of the strategy work together in important ways. In particular, many of the planned activities can be seen as enhancing and consolidating vaccine demand from MICs, which, in conjunction with interventions on the supply side, will help give MICs

access to more affordable and secure supply, the strongest area of concern. Access to more affordable supply can in turn allow countries for which vaccine prices have been an obstacle to introduce and sustain coverage of needed vaccines.

The non-Gavi MICs are a diverse group with varying needs. The Task Force therefore designed the strategy as a menu of options, from which countries will be able to choose the kinds of assistance that they identify as priorities. In providing this assistance, the strategy would emphasize collaboration among MICs and peer-to-peer learning. This and other aspects of strategy implementation will require innovation in the way participating organizations work to enable greater collaboration and flexibility.

Acting as secretariat of the Task Force, WHO has estimated the total cost of the support activities included in the MIC Strategy and evaluates this investment at approximately $20 million per year for the 2016-2020 period. This relatively low cost reflects the strategy's focus on targeted technical assistance to remove important obstacles while relying heavily on countries own resources to achieve their immunization goals. The Task Force is also exploring innovative approaches to increasing the credibility and market impact of MICs vaccine funding. This mechanism, which could involve a development bank, would be based primarily on the budget commitments of participating countries and would thus depend critically on country commitment. The Task Force will proceed with assessing the cost effectiveness aspect of the funding needs once the visibility to country demand improves.

The proposed MIC Strategy will be discussed at the SAGE meeting in April 2015 and subsequently fine-tuned in light of feedback and further consultation with countries, regions, and immunization partners. The Task Force will also begin discussions with potential donors and, if there is sufficient interest in supporting the strategy, turn to developing a detailed implementation plan.

Background

Over the past decade, access to vaccines in middle-income countries (MICs) has become a much debated issue. At the heart of the "MICs issue" is the reality that two thirds of the world's poor now live in MICs. This is a dramatic change from the 1990s when 93% of poor people lived in low-income countries (LICs).[1] This issue has also been viewed through the lens of global disease burden and immunization performance: MICs account for 60% of global under-five deaths, as well as similar or greater shares of vaccine-preventable deaths and unvaccinated children (DTP3).[2,3,4]

In the immunization field, an important impetus for a MICs focus has been a concern that these countries, excluded from or facing the loss of donor support, may be missing out on opportunities to introduce important vaccines. The World Health Assembly (WHA) and the WHO Strategic Advisory Group of Experts on immunization (SAGE) have repeatedly called upon the WHO secretariat and the international community to more rigorously investigate obstacles to and mobilize resources for sustainable access to vaccines in MICs.[5] Also, the Global Vaccine Action Plan (GVAP)—endorsed by WHA in 2012—calls for innovation in pricing and procurement models for MICs. The cause of these countries has been championed by the regions of the Americas, Europe and the Eastern Mediterranean.

As the MIC issue gained the attention of immunization agencies, SAGE recognised the increased response. Yet, in November 2012, SAGE pointed to the absence of a clear strategy and action plan in this area and warned that it could lead to ineffective and inefficient use of scarce resources and an inequitable focus on some geographical areas.[6]

The MIC Task Force

In light of these trends and in response to the SAGE recommendation, the WHO secretariat convened a Task Force on sustainable access to vaccines in MICs in June 2014 and tasked it with: i) reviewing the performance of MICs in immunization; ii) refining understanding of the needs of MICs and taking stock of ongoing activities to address these needs; iii) defining a shared strategy, action plan, and monitoring and evaluation framework to enhance sustainable access to vaccines in MICs; iv) acting as an information-sharing and coordination forum across immunization agencies active in MICs. The Task Force is intended to be an inclusive forum for engaging stakeholders as well as a mechanism for generating political will.

Several agencies are represented in the MIC Task Force: the Agence de Médecine Préventive, the Bill and Melinda Gates Foundation, the Gavi Secretariat, the Sabin Vaccine Institute, the Task Force for Global Health, UNICEF Programme and Supply Divisions, WHO (headquarters, PAHO/AMRO, EURO, and EMRO) and the World Bank. (For details on membership, see Annex I.) The work of the MIC Task Force is supported by the Bill and Melinda Gates Foundation, which is also funding analytical work by the Results for Development Institute in support of the Task Force.

[1] Poverty and Inequality World Bank database (2011). Also see: Sumner A (2012): "Where Do The World's Poor Live? A New Update", IDS WORKING PAPER Volume 2012 No 393, and Glassman A, Duran D, Sumner A (2011): "Global health and the new bottom billion: what do shifts in global poverty and the global disease burden mean for Gavi and the Global Fund?". Center for Global Development, Working Paper 270.

[2] Results for Development analysis, 2014.

[3] These realities reflect in part the shortcomings of the Gross National Income (GNI) per capita measure used to define these country income categories—and to determine eligibility for many forms of international assistance. This measure both fails to capture many aspects of development status and ignores altogether how income and the fruits of development are shared.

[4] Levine O, Bloom D, Cherian T, De Quadros C, Sow S, Wecker J, Duclos P, Greenwood B (2011): The future of immunisation policy, implementation, and financing. Lancet, pp55-56.

[5] SAGE November 2008, 61st WHA May 2008, SAGE November 2010.

[6] SAGE Meeting, November 2012, Meeting Report http://www.who.int/wer/2013/wer8801.pdf?ua=1 (accessed 13.05.2014).

Since its inception, the MIC Task Force has met over teleconferences and in person. In addition, the Task Force has conducted consultations with countries, CSOs, industry, and partners.[7] The Task Force's findings and recommendations have been presented at the SAGE GVAP working group in March 2015 and will be discussed at SAGE in April 2015.

Re-assessing the "MICs issue"

In the past, analysis of MICs performance in immunization has been framed in terms of rate of new vaccine adoptions compared to donor funded LICs. In order to gain additional clarity on the nature of the problem, the Task Force reviewed the performance of all 103 middle-income countries[8] against GVAP targets for which data were readily available. The Task Force believed a comparison against agreed absolute standards would be more meaningful and ambitious than relative comparison of MICs to LICs. Also, using the GVAP framework, rather than studying new vaccine introductions alone, allows a more comprehensive understanding of MICs performance.[9] Full results of the analysis performed will be presented at SAGE in April 2015 and available thereafter on the SAGE website.

In brief, the analysis showed that, overall, MICs have considerable work to do to meet the GVAP Decade of Vaccines targets:

i) Almost 90% of polio cases in 2014 were in MICs: there were cases in Pakistan, Nigeria, Iraq, Syria, and Cameroon;
ii) India, Nigeria, Indonesia, Algeria, Zambia still suffer considerable measles deaths, while Nigeria, China, India, Indonesia, Pakistan, and Angola had the highest number of reported cases in 2013;
iii) Only 19 MICs, including China and Egypt, have reduced under-five mortality by two thirds since 1990;
iv) 38 MICs have DTP3 coverage below 90% and more than half fail to meet targets for coverage equity;
v) 20% of MICs had not introduced any of six priority new or underused vaccines by the end of 2013;[10]
vi) Trends in domestic expenditure fall short of targets and, finally;
vii) Only about 40% of MICs have functional national technical advisory bodies on immunization ("NITAGs").[11]

The re-assessment also highlighted that there is significant heterogeneity across the entire group of MICs and that a more granular assessment is warranted. This analysis showed that; i) no sub-group of MICs, defined by region, income, or Gavi status, is meeting all GVAP targets; ii) the great majority of vaccine-preventable deaths are in Gavi countries, particularly India and Nigeria, but also poorer Gavi-eligible MICs; iii) the American and European regions are the best performers; iv) non-Gavi MICs are on average performing better than Gavi-supported MICs; v) upper-middle-income countries are performing consistently better than lower-middle-income countries.

Given past concern that MICs might be lagging behind donor-funded LICs in new and priority vaccine introduction, the Task Force looked carefully at this issue while recognizing the limits of such assessment. The Task Force concluded that while the MICs as a group do lag in the fraction of children reached with some important new vaccines, notably the pneumococcal conjugate and

[7] Two regional consultations were organised (EUR and EMR) as well as meetings with CSOs and industry associations (IFPMA, DCVMN). Partners have also been surveyed.
[8] Based on World Bank definition of countries with gross national income (GNI) per capita of US 1,046 to 12,745.
[9] For instance in recognition of country independent decision making vis-à-vis new vaccine introductions also based on local mortality/morbidity and cost- effectiveness considerations.
[10] These vaccines are PCV, rotavirus, HPV, IPV, Japanese encephalitis, and yellow fever.
[11] As assessed by compliance with six indicators on the WHO/UNICEF joint reporting form.

rotavirus vaccines, this lag is driven primarily by a few large countries. These large countries—with the exception of China—are still Gavi-supported and include India, Nigeria, Indonesia, and Pakistan.

The Task Force believes that this analysis represents an important reframing of the so-called "MICs issue": the challenges MICs face in reaching globally agreed immunization targets are real, but these challenges are not well captured by the notion that these countries have fallen behind donor-supported countries.

Scope of a MIC Strategy

Faced with developing a coherent strategy for action and making the best use of limited resources, the Task Force agreed to use the following principles to drive its own recommendations on scope and priorities: maximize health impact, maximize value for money, address inequities within and among countries, consider technical and political feasibility, and complement existing and planned efforts.

With these principles in mind, the most important decision that the Task Force made was to focus its efforts on MICs not receiving support from Gavi. Although the 40 Gavi MICs currently have the greater share of vaccine-preventable disease burden (88%), they are well supported to address this burden and to move toward the GVAP goals. In contrast, the remaining 63 MICs benefit neither from major donor support nor from a unified international strategy. These countries are where the MIC Task Force can have the greatest impact.

The non-Gavi MICs shares of people living in poverty, disease burden, unimmunized children, while relatively modest as a fraction of the global total, are nonetheless considerable, and unacceptable as well as a challenge to GVAP's elimination goals. China, Brazil, and South Africa are among the top 20 countries in numbers of people living on less than $1.25/day.[12] There are an estimated 152,000 vaccine-preventable deaths in non-Gavi MICs every year. Globally, non-Gavi MICs represent 20% of pneumococcal pneumonia cases, 10% of resulting mortality, and 13% of pneumonia DALYs. Of these cases, 75% occur in countries that have not introduced PCV, while 67% of deaths in non-Gavi MICs happen in countries without PCV.[13] These countries also represent 28-32% of global cervical cancer mortality and morbidity.[14] About 2.6 million children in these countries fail to receive all three doses of DTP, 2.4 million are not immunized against measles, and almost 32 million do not receive three doses of PCV. Some non-Gavi MICs have unacceptably low coverage rates. Eight countries, with a total birth cohort of 2.7 million, have below 80% national MCV1 coverage,[15] and six have below 80% DTP3 coverage.[16]

These countries, in general, have stronger health systems and immunization programs than poorer countries, making rapid gains possible if critical obstacles were removed. Moreover, as non-Gavi MICs include 30% of the global birth cohort, strengthening the capacity of these countries to introduce new vaccines and increase coverage could help to consolidate vaccine demand and contribute to healthy markets, potentially benefiting Gavi and non-Gavi MICs alike.

The Task Force also recognised that the non-Gavi group of MICs would change over time, with up to 24 countries possibly losing Gavi support by 2020. The share of vaccine-preventable deaths in MICs occurring in countries not receiving Gavi support is likely to grow from 12% in 2014 to 37% in 2020 and possibly as much as 82% in 2025.[17] While the Task Force agreed that Gavi is best placed to

[12] Andy Sumner (2012): "Where Do The World's Poor Live? A New Update", IDS WORKING PAPER Volume 2012 No 393.
[13] Mortality from WHO CHERG data. Morbidity source: TRIVAC v. 2.0 (dataset includes 183 countries), based on unpublished, country-level 2008 Global Burden of Disease estimates.
[14] GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11
[15] WUENIC coverage data, 2013. Vanuatu, Syria, Iraq, South Africa, Marshall Islands, Gabon, Lebanon, Dominican Republic (in order of lowest to highest coverage).
[16] WUENIC coverage data, 2013. Marshall Islands, Syria, South Africa, Vanuatu, Iraq, Gabon (in order of lowest to highest coverage).
[17] India, Nigeria, Pakistan, and Indonesia are projected to have graduated from Gavi support by this date.

support eligible and graduating MICs, it concluded that graduated countries should be fully in its scope and that the MIC Strategy should seek to anticipate and address the needs of these countries after the end of Gavi support.[18] Thus, in focusing on non-Gavi MICs, the Task Force aims to address the needs of a group of countries that, over the medium and long term, may grow to encompass most of the world's poor and many of the greatest immunization challenges.

Reflecting the GVAP goals and its own analysis of the potential contribution of increased coverage to alleviating the burden of vaccine-preventable disease, the Task Force also agreed that it was important to address both new vaccine introduction and coverage of existing vaccines. This choice was further supported by consultations with countries and WHO regional offices.

Finally, the Task Force agreed to work on two time horizons. For a first period aligned with the GVAP timeframe (2015-2020), the Task Force developed a detailed strategy to help non-Gavi MICs, possibly including a first set of Gavi-graduated countries, to reach GVAP targets. For a second period (2021-2025), the Task Force proposes to develop as necessary an adapted strategy accounting for changes in the immunization and development landscape. These changes could include a new global vision of immunization beyond GVAP, graduation of new countries from Gavi (and perhaps exit of some countries from middle-income status), and possibly a new country classification framework for determining allocation of donor support relying less on GNI per capita.[19]

Focus of a MIC Strategy: needs, gaps, and solutions

The MIC Task Force has analysed the needs of non-GAVI MICs, assessed current efforts by international partners to meet these needs, and identified remaining gaps. A detailed description of sources used for this work is provided in Annex II. A detailed mapping of current ongoing partner efforts in MICs is available in Annex III.

The Task Force's review suggests that the most important unmet needs for these countries are in four main areas: i) Evidence-based decision-making; ii) Political will and national immunization financing; iii) Demand for and delivery of immunization; and iv) Access to timely and affordable vaccine supply. Based on this analysis, the group has developed a package of activities that could be offered to countries. These activities, along with coordination mechanisms, targets and indicators, as well as timelines, constitute the proposed MIC Strategy. The draft strategy is summarized in tabular form on page 16 of this report; more details on the proposed activities can be found in Annex IV.

It is important to note that the activities proposed for the MIC Strategy, which are described in the following sections, are a mixture of existing activities that can be expanded to help additional countries and a few key new initiatives. Of note, much of the debate on access to vaccines in MICs has focused on prices. While the Task Force recognizes the crucial importance of affordability as an obstacle, especially to new vaccine adoption, it believes that a more comprehensive approach that addresses coverage as well as new vaccine introduction and promotes affordability through both supply and demand-side measures is more likely to be productive.

1- Strengthened decision making for timely and evidence-based immunization policy

Informed decision-making on vaccine introduction and other areas of immunization policy is crucial for all countries, but particularly important for countries that fully fund their immunization

[18] The Task Force also recognized that the global community may have a responsibility to monitor and support Gavi's efforts to ensure successful graduation. It agreed that graduating countries would be 'watched', and the Task Force would remain available to play a role should the Gavi Alliance identify any added value in its engagement.

[19] Saez, Catherine. "New Quiet Initiative To Improve Drug Access In Middle-Income Countries, Change Country Classification System." *Intellectual Property Watch*. 25 February 2015. Available at: http://www.ip-watch.org/2015/02/25/new-secret-initiative-to-improve-drug-access-in-middle-income-countries-change-country-classification-system/ (last accessed 03/03/2015).

programmes.[20] In these countries, adoption and related decisions are likely to be more country-owned and less reliant on international recommendations, and strong cases need to be made to secure sufficient domestic resources to sustainably fund programmes.

Immunization partners have agreed that NITAGs are important structures of the decision making process, while recognizing that NITAGs are not always sufficient for sound decision-making. GVAP calls on all countries to put in place functional NITAGs by 2020, yet in 2013 only 38% of non-Gavi MICs had done so.

Although a sound decision-making process can result in a decision not to adopt a WHO-recommended vaccine, as justified by local epidemiological, economic, or other considerations, such a process can ensure that recommended vaccines are promptly and rigorously considered for national introduction and that, where introduction is warranted, a strong case is made to policy-makers.[21] Recognizing country ownership of vaccine adoption decisions, GVAP also calls on countries to introduce one or more new or underutilized vaccine by 2020. As of December 2013, 34 non-Gavi MICs representing 54% of countries in the group and 64% of the group's birth cohort have adopted one or none of six high-priority new vaccines analysed.[22] Fourteen non-Gavi MICs, accounting for 22% of countries and 6% of the group's birth cohort, have adopted none of the six vaccines.

Several partners are active in strengthening national decision-making processes through supporting evidence-based policy recommendations, disease burden measurement, economic analysis, tools development, training, advocacy, technical assistance, and recent analyses have documented the impact of these efforts.[23,24] While global efforts in this area can benefit all countries, targeted country efforts are currently limited to Gavi or PAHO countries, leaving a clear gap for non-Gavi MICs. Recognizing this gap as well as the availability of active initiatives and tested tools to address this need, the MIC Task Force proposes to build on current efforts and past experience to extend services to a broader range of non-Gavi MICs.

Strengthened decision-making on immunization policy plays a crucial role in the overall MIC Strategy, as it underpins—and logically precedes—mobilization of domestic political will and financing, contributes to increased and more credible demand for vaccines (and thus lower prices), and supports efforts to strengthen immunization systems and combat hesitancy. The relationship between the different arms of the strategy is discussed at greater length in the last section of the report.

2- Increased political commitment & financial sustainability of immunization programmes

Non-Gavi MICs must rely primarily or exclusively on domestic resources to purchase vaccines and fund immunization services. Inadequate national financing—in some cases reflecting insufficient political will— as well as inefficient use of available resources may limit both new vaccine

[20] It is important to recognize that NITAGs should advise not only on introduction of new vaccines but also on optimization of existing schedules and other aspects of immunization policy.

[21] Countries may decide not to introduce a vaccine because they believe disease burden is relatively low, or because other interventions are a more appropriate or cost-effective way to address the burden. Many MICs have more effective health systems and thus curative services than most LICs, which may reduce the potential benefit of some vaccines. Finally, countries may decide not to introduce some useful vaccines because they are not cost-effective or affordable at current prices. Decisions made on this basis could be reversed if countries had access to lower prices.

[22] PCV, rotavirus, HPV, IPV, Japanese encephalitis, and yellow fever. Year of introduction of selected vaccines, as of 31 December 2013. Immunization, Vaccines and Biologicals, World Health Organization. Database available for download at: http://www.who.int/immunization/monitoring_surveillance/data/en/.

[23] Adjagba, A., Senouci, K., Biellik, R., Batmunkh, N., Faye, P. C., Durupt, A., ... & da Silva, A. (2015). Supporting countries in establishing and strengthening NITAGs: Lessons learned from 5 years of the SIVAC initiative. *Vaccine*, 33(5), 588-595.

24 For more on strengthening country-level decision-making, please see: Jauregui, B., Sinha, A., Clark, A. D., Bolanos, B. M., Resch, S., Toscano, C. M., ... & Andrus, J. K. (2011). Strengthening the technical capacity at country-level to make informed policy decisions on new vaccine introduction: lessons learned by PAHO's ProVac Initiative. Vaccine, 29(5), 1099-1106.

introduction and immunization coverage. This issue has been raised several times by countries and agencies in the context of MIC Task Force consultations.

Data on domestic immunization expenditures in non-Gavi MICs are limited in coverage and quality, and the Task Force recognized the need to work more intensively with MICs on tracking resources and documenting budget performance. The available data demonstrate, however, that the share of government resources devoted to the purchase and delivery of vaccines varies widely across MICs, from a maximum of 0.47% of general government expenditure (GGE) in Paraguay to a minimum of 0.01% in China. There is no currently agreed target level for domestic financing, but if the median share of GGE spent on vaccines in the PAHO region (0.06%) is taken as a benchmark, 35 non-Gavi MICs, representing 72% of the group's birth cohort, currently fail to meet this standard.[25]

In addition, GVAP calls for all countries to have standard budget line items for vaccines and immunization programmes in their national or health sector budgets, which can contribute to higher and more predictable immunization funding.[26] Almost all non-Gavi MICs (54 of 63) have met this target,[27] but only 46% of non-Gavi MICs have increased domestic expenditure on immunization, as required by a second GAVP target.

Finally, consultations with WHO regions strongly reinforced the importance of helping countries to mobilize additional domestic resources for immunization as well as the scope for using resources more efficiently.

Several agencies support countries to enhance national funding to immunization through advocacy, technical assistance, peer exchanges, and training, but, here again, these activities primarily benefit Gavi or PAHO countries.[28] Drawing on existing expertise and tools, the Task Force proposes to expand existing services to non-Gavi MICs.

3- Enhanced demand for & equitable delivery of immunization services

In addressing coverage, the Task Force further noted that both the delivery of immunization services—the reach and efficiency of programmes—and demand for these services were important, especially in light of growing concerns over vaccine hesitancy. It therefore proposes activities in both areas.

Addressing Vaccine Hesitancy and Building Community Demand for Vaccines

In order to achieve and maintain high uptake, the vaccine community needs to sustain both public and provider confidence in vaccines and their benefits. "Vaccine hesitancy", which refers to delay in acceptance or refusal of vaccines despite availability of vaccination services, has been flagged as an area of concern since 2011.[29] A recent SAGE Working Group on the issue noted that hesitancy is complex and context-specific and is influenced by factors such as complacency, convenience and

[25] This is an illustrative example to demonstrate how a benchmark might be used in practice. The American region was chosen as a benchmark for its high performance in vaccine coverage and introduction of new and under-utilized vaccines. Health spending was calculated as a percentage of 2012 GGE using data from 2012 Joint Reporting Forms and the IMF's *World Economic Outlook* database. This analysis excludes nine non-Gavi MICs due to insufficient data (Iraq, Libya, Maldives, Mexico, Micronesia, Montenegro, Palau, Serbia, and Syria).

[26] Lydon et al (2008) Government financing for health and specific national budget lines: The case of vaccines and immunization. *Vaccine* 26: 6727-34. Available at: http://www.who.int/immunization/programmes_systems/financing/analyses/JVAC_8255_LydonP.pdf.

[27] Joint Reporting Forms, 2013.

[28] McQuestion, M., Gnawali, D., Kamara, C., Kizza, D., Mambu-Ma-Disu, H., Mbwangue, J., & de Quadros, C. (2011). Creating sustainable financing and support for immunization programs in fifteen developing countries. *Health Affairs*, *30*(6), 1134-1140. Information on EURO's work with graduating countries was obtained from Osman Niyazi Cakmak, MIC Task Force member.

[29] WHO (2012). Meeting of the Strategic Advisory Group of Experts on Immunization, November 2011 – conclusions and recommendations. *Weekly Epidemiological Record*, 87, 1-16.

confidence.[30] SAGE recognized that this is a rapidly changing global problem that requires global attention and has called for countries to establish the capacity to deal with hesitancy and for partners to support them.[31]

While it is currently difficult to measure and locate vaccine hesitancy and thus quantify the extent of the problem in non-Gavi MICs, country consultations confirmed that vaccine hesitancy is an important concern that could jeopardize sustained vaccine coverage of existing vaccines as well as new vaccine introductions. People in MICs, like those living in high-income countries, have better access to curative medicines and are thus less likely to die of communicable diseases than people in LICs. This is likely to be one of the factors eroding the perceived benefit of immunization. In addition, MICs tend to adopt similar practices to HICs and are thus influenced by hesitancy behaviours we are witnessing in richer settings.[32]

While there are various country-level attempts to address vaccine hesitancy, there are few international initiatives. The European Regional Office (EURO) has begun to work in this area through technical assistance, guidelines and tools (Tailoring Immunization Programmes – TIPs tool) based upon evidence from behavioural economics, the medical humanities, psychology, and neuroscience.[33] The London School of Hygiene and Tropical Medicine has created a Vaccine Confidence Index, which is a global surveillance tool to identify and track rumours and misinformation related to immunization.[7] Most of this work though is only at its inception and currently focuses on HICs or LICs.

Given remaining gaps globally and for MICs in particular, the MIC Task Force proposes to make this a core area of the MIC Strategy, building organizational capacity, conducting research, and developing tools in line with the SAGE recommendations. The Task Force believes that hesitancy may be easier to understand and managed in institutionally stronger MICs than in low-income settings and results of this work could benefit LICs and HICs alike.

In-country supply chain & data systems

Given the complexity of immunization systems and the need to limit the number of activities in the strategy, the Task Force chose to focus on two areas on the delivery side that stood out in country and partner consultations and which seemed particularly amenable to international assistance: supply chain and data systems.

According to data on wastage rates, stock-outs, and coverage, and scores on WHO Effective Vaccine Management (EVM) assessments, the Task Force estimates that at least 28 non-Gavi MICs, representing 32% of the birth cohort, face supply chain issues.[34] MICs are facing significant challenges in their vaccine logistics systems, given the burden of introducing new vaccines that are often more costly and require greater storage capacity. Countries have to properly manage smaller, but sufficient stockpiles, reduce wastage, accurately forecast vaccine requirements, and prevent

[30] Report of the SAGE Working Group on Vaccine Hesitancy. 1 October 2014. Available at: http://www.who.int/immunization/sage/meetings/2014/october/1_Report_WORKING_GROUP_vaccine_hesitancy_final.pdf.
[31] SAGE MICs report.
[32] More information on consultations is available upon request.
[33] EURO. "European Immunization Week – Guidelines for national planning. Available at: http://www.euro.who.int/__data/assets/pdf_file/0003/84297/EIW2011_guidelines_update.pdf?ua=1. Since Bulgaria established TIP in 2012, the Ministry of Health has developed plans to introduce new tools to strengthen the quality of discussion regarding immunization between general practitioners and families, to improve curricula and training of Roma health mediators to optimize their role in promoting immunization, and to revise the school-entry vaccination policy and develop lessons on vaccines and infectious diseases. See EURO. "TIP implementation in Bulgaria." Available at: http://www.euro.who.int/en/health-topics/communicable-diseases/poliomyelitis/activities/tailoring-immunization-programmes-to-reach-underserved-groups-the-tip-approach/tip-country-projects/tip-implementation-in-bulgaria.
[34] This number includes countries with a third or more blank responses on the 2013 JRF; those that do not report having a systems for monitoring adverse events; and those with a high share (60% or greater) of private health expenditure.

equipment breakdowns. Embedded in this issue is a need to strengthen human resources and the training and motivation of supply chain workers to ensure competency and low turnover rates.[35]

Similarly, country consultations revealed that health information systems are weak in many MICs. Basic data, for example on immunization coverage or vaccine needs and stocks, are often not reliable or available in a timely manner, and are not always well used by managers to improve performance. The result could be lower coverage, either because unreached populations are not identified or because of vaccine distribution problems.[36]

Based on a number of criteria, including incomplete reporting on the JRF, lack of an adverse events monitoring system, and high reliance on the private sector for health service delivery, the Task Force estimates that 46 non-GAVI countries, representing 84% of the birth cohort, may benefit from assistance with data systems.[37]

Various agencies are currently working in these areas, according to the Task Force's mapping, but few are working in non-Gavi MICs. The Task Force proposes to make use of these existing initiatives and tools and to focus particularly on human resource strengthening—helping countries to improve their own capacity to manage data and supply chains. The Task Force proposes to achieve this to a large extent through peer-to-peer learning. Two areas of focus might be data systems in rapidly growing urban areas, a particular concern for many MICs, and the implementation of electronic immunization systems, where guidance is badly needed. Electronic immunization systems that are linked with civil registries have contributed significantly in improving immunization data quality in the European region.[38]

4- Improved access to affordable and timely supply

The affordability of new vaccines, especially for non-Gavi MICs and countries soon to lose Gavi support, has been a big concern for the past few years. [39] At the 67th World Health Assembly in 2014, dozens of countries requested greater price transparency, information on cost of production, support for improving negotiation capacity, and access to lower prices.[40] The limited price information that is available shows a wide variation in prices currently paid by non-Gavi MICs and consultations conducted by the Task Force confirmed that prices are one of the main preoccupations of countries.[41]

In these consultations, countries also raised the issue of sustained access to supply: indeed, according to the 2014 GVAP assessment report, 40% of low- and middle-income countries have

[35] Zaffran, M., Vandelaer, J., Kristensen, D., Melgaard, B., Yadav, P., Antwi-Agyei, K. O., & Lasher, H. (2013). The imperative for stronger vaccine supply and logistics systems. *Vaccine*, *31*, B73-B80. Available at: http://www.who.int/immunization/sage/meetings/2013/november/3_stronger_vaccine_supply_and_logistics_systems.pdf

[36] PATH. "Fact Sheet". *Better Immunization Data Initiative.* Available at: http://bidinitiative.org/wp-content/uploads/BID_factsheet_02_Final.pdf

[37] This number includes countries with a third or more blank responses on the 2013 JRF; those that do not report having a systems for monitoring adverse events; countries that do not meet the district coverage equity target; those with less than 80% coverage of MCV1 and DTPs; those with more 50% urban population; and those with a high share (60% or greater) of private health expenditure.

[38] In Georgia, electronic registries are integrated with the civil registries and have managed to reach 15% more children that were not captured before. Most EUR countries that have established immunization registries are able to collect data on vaccines, generate reminders and recall vaccination notices for each client, provide official vaccination forms upon request, and allow vaccination coverage assessments. See Johansen, K., Lopalco, P. L., & Giesecke, J. (2012). Immunisation registers–important for vaccinated individuals, vaccinators and public health. *Euro Surveill*, *17*(16), 2-4.

[39] Médecins Sans Frontières (2015). Right Shot: The Right Shot: Bringing down barriers to affordable and adapted vaccines. Available at: http://www.msfaccess.org/content/right-shot-bringing-down-barriers-affordable-and-adapted-vaccines.
Makinen, M., Kaddar, M., Molldrem, V., & Wilson, L. (2012). New vaccine adoption in lower-middle-income countries. *Health policy and planning*, 27(suppl 2), ii39-ii49.

[40] WHA67.

[41] V3P. Database, reports, and analyses. Available at: http://who.int/immunization/programmes_systems/procurement/v3p/platform/database/en/.

suffered national-level stock-outs of at least one vaccine that lasted at least one month. Twenty-one non-Gavi MICs experienced such stock-outs, accounting for 15% of all the low- and middle-income countries with national level stock-outs. Non-Gavi countries are also struggling to secure supply for new vaccine introductions and reported difficulties securing responses to tenders for new introductions.[42]

As mentioned above, in recent years the tendency has been to consider the issue of access to affordable and timely supply for MICs in isolation, and several initiatives have been launched recently to address it, including UNICEF's MICs tender and WHO's Vaccine Price, Product Procurement initiative (V3P). The MIC Task Force has concluded that a more comprehensive approach that addresses both demand and supply-side constraints to affordable supply is more likely to bear fruit. This broader approach would nevertheless include activities more specifically focused on price and supply (see below).

Increasing procurement skills and knowledge

Previous studies have identified inefficient procurement as an important barrier to MICs obtaining competitive prices and reliable supply of new and traditional vaccines.[43] Technical assistance on procurement options and practices is a way to improve the efficiency of procurement, especially in self-procuring countries (currently 16 non-Gavi MICs including 11% of the non-Gavi MICs birth cohort), but also in mix-procuring countries. It is important to recognize that inefficient procurement can reflect deep-seated deficiencies in public-sector management or corruption.

A few organizations are currently helping MICs improve procurement practices, the effort is very limited due to unclear roles and responsibilities, limited capacity and country scope. This is an important area where the Task Force is determined to increase effort though a collaboration among UNICEF, WHO and possibly the World Bank to strengthen procurement knowledge and skills. The Task Force proposes to do this through increased peer learning among countries, development of missing tools (such as updated procurement guidelines) and provision of targeted technical assistance to countries most in need.

Access to price and contract information

Vaccine price is a major factor in deciding whether and when to adopt new vaccines. Without information on prices paid by comparable countries—and information on contract terms—decisions about vaccine adoption are often delayed or misinformed.[44] Price transparency is also a way for countries to ascertain whether they are paying equitable prices. Analysis of national price databases and other medicine price mechanisms have shown positive effects on access to medicines, including the uptake of higher quality medicines, more favourable results from contract negotiations, changes in national pricing policies, and decreased prices.[45]

Information on vaccine prices is particularly important for self-procuring MICs countries, which deal directly with manufacturers and have limited financial resources available for vaccine purchase.

There are currently four main initiatives—UNICEF's and PAHO's publication of prices awarded in their vaccine tenders, WHO's V3P, and MSF's advocacy and analysis on vaccine prices[46]—aimed at

[42] EMRO or EURO MIC Task Force country consultations. More information available upon request.
[43] Makinen et al (2012) New vaccine adoption in lower-middle income countries. *Health Policy and Planning* 27: ii39-ii49.
[44] Results for Development, Inc. (2011). Synthesis Report of New Vaccine Adoption in Low-Middle Income Countries (available at http://www.who.int/immunization/programmes_systems/financing/analyses/Obstacles_to_New_Vaccine_Adoption_in_LMICs.pdf).
[45] Hinsch, M., Kaddar, M., & Schmitt, S. (2014). Enhancing medicine price transparency through price information mechanisms. *Global Health*, *10*, 34.
[46] MSF. (2015). *The Right Shot: Bringing down barriers to affordable and adapted vaccines*. Available at: http://www.msfaccess.org/content/right-shot-bringing-down-barriers-affordable-and-adapted-vaccines.

giving countries more information on vaccine prices. Given recent investment in these initiatives and broad political support for their implementation (e.g. SAGE 2014),[47] the Task Force believed they should continue as part of a broader MIC Strategy.

Access to revolving funds

Assurance that suppliers will be paid on time is important to obtain lower vaccine prices, but some MICs face uncertainties in their annual budgetary allocation processes that make it difficult to ensure timely payment. Some also have legal restrictions on prepayment, while others cite access to hard currency as a barrier.[48]

Revolving funds such as PAHO's and the UNICEF Vaccine Independence Initiative (VII) provide a line of credit to member countries unable to produce funding for a vaccine purchase at the time needed, allowing countries greater flexibility in payment terms and preventing supply disruptions. It should be noted that a revolving fund only addresses timing issues: if countries do not repay in full, the revolving fund will not be sustainable. The PAHO Revolving Fund credit line is available to all participating countries and territories in the AMR region, but cannot be expanded to other regions. UNICEF's VII is currently used by 18 countries (four countries and 13 Pacific Islands) due to a small capital base. The VII has had only one default in its 24-year history.[49]

Even with these funds, there is a large unmet need for pre-financing support. UNICEF SD has generally received, on average, $100 million worth of pre-financing requests annually. More than half of the requests are for immunization supplies, and the majority of requests are unmet. By 2020, UNICEF SD expects to receive more than $225 million in pre-financing requests annually, 75% of which will continue to be for immunization-related commodities.[50]

A solution to payment issues in MICs could be to give more MICs the option to draw on revolving funds. A recent UNICEF Executive Board decision has authorized expansion of VII's capital base to $100 million,[51] provided sufficient resources become available. There is great potential for VII to benefit many more countries. In line with this opportunity, the Task Force proposes to continue existing efforts in this area.

Product registration requirements

Inefficient and widely varying processes for registering vaccines, including WHO-prequalified vaccines, create an important obstacle to the introduction of new vaccines, lengthening timelines and driving up costs for countries and suppliers. The barrier that distinct and sometimes onerous registration requirements pose is almost certainly greater for lower-cost manufacturers (who have fewer in-country staff to negotiate these processes).[52] At a minimum, 30 non-Gavi MICs, representing 48% of countries, could benefit from streamlined regulatory processes to expedite

[47] Through the 2014 GVAP report, SAGE recommends that: i) countries change the rules of the game on vaccine affordability, to create transparency which is in their interest. They can do this by making pricing information publicly available, and by collaborating with WHO and all technical agencies to develop solutions; ii) technical partners support countries to improve the transparency of vaccine pricing. Technical agencies themselves should do everything possible to share pricing data. This report is available at: http://www.who.int/immunization/global_vaccine_action_plan/SAGE_DoV_GVAP_Assessment_report_2014_English.pdf?ua=1.
[48] Gavi. Country needs assessment of Access to Appropriate Pricing for Gavi graduates and non-Gavi LMICs.
[49] UNICEF. "Vaccine Independence Initiative (VII)." Available at: http://www.unicef.org/pacificislands/immunization_2881.html.
[50] UNICEF (2015). Executive Board first regular session. "Recommendation to the Executive Board: Extension and expansion of the Vaccine Independence Initiative and its revolving fund". Available at: http://www.unicef.org/about/execboard/files/2015-PL5-VII_and_revolving_fund-ODS-EN.pdf.
[51] UNICEF. VII and Revolving Fund Expansion: Informal Board Session. January 2015. Presentation available at: http://www.unicef.org/about/execboard/files/VII_Expansion_Informal_Board_2015_01_20.pdf.
[52] Consultation with DCVMN at annual conference, November 2014.

access to prequalified and other priority vaccines.[53]

The Task Force discussed possible solutions to this issue, taking into account on-going initiatives to establish global norms and standards, understand regulatory pathways, and align regulatory requirements and pathways, while recognizing their limitation in geographic or vaccine scope. The Task Force proposes to focus over the long term on continued efforts to streamline and align requirements for vaccine registration regionally and globally, which would alleviate these constraints while preserving country autonomy.[54] In the shorter term, expedited processes for prequalified vaccines could be a useful compromise.[55] The recent experience with facilitating introduction of IPV as part of the Polio Endgame, during which the WHO Regulatory Strengthening and Vaccine Assessment Prequalification teams coordinated efforts to ensure timely registration of prequalified vaccines in some countries, was well received by both countries and manufacturers.[56]

Pooled procurement and access to external procurement services

External procurement services, for example through UNICEF Supply Division, can be a useful option for MICs that have limited procurement capacity. When the use of external procurement services also allows pooling of demand, it can help smaller countries that lack the individual market power to generate competitive bids. Even for large countries, pooled procurement can in theory provide greater market leverage and better access to reliable, affordable supply. The use of external procurement services can also help suppliers by eliminating the need to negotiate separately with each country. The Task Force recognises that not all countries will choose this option and that countries will use external procurement services in different ways. Some countries currently choose to use the UNICEF Supply Division or the PAHO Revolving Fund (see below) as routine channels for vaccine procurement, while others make use of these services on an ad hoc basis (for instance as procurement agent of last recourse if unable to access sufficient quantities of vaccine). Some countries see the use of external procurement services, including pooled procurement, as a long-term strategy, as is the case for many countries in the Americas region, while others may see it as short-term expedient as they build their own procurement capacity.

The use of external procurement services could benefit a wide variety of non-Gavi MICs outside the Americas region (where pooled procurement through PAHO is already the norm for many countries), including fully self-procuring MICs, MICs that use 'mixed procurement modalities', and small MICs with low bargaining power. In addition, countries that already procure individually through UNICEF could gain additional benefits from pooled procurement, if the barriers to effective demand consolidation could be overcome. Overall this covers all countries outside of PAHO (43) representing 68% of non-Gavi MICs and 77% of the group's birth cohort.[57]

There are currently several initiatives in this area. The PAHO Revolving Fund for the Americas region, which combines pooled procurement with a revolving fund line of credit and technical assistance to countries, remains one of the most successful and well-known examples of pooled procurement. The Revolving Fund has increased the accuracy of vaccine demand forecasts and ensured timely

[53] Estimate of countries in need was developed through conversations with WHO HQ/HIS/EMP/RHT/RSS team. Estimated range: 30-50 non-Gavi MICs (48-79% of countries).
[54] This includes required information in dossiers, registration procedures and perhaps also other aspects of the process.
[55] In principle these measures would allow vaccines to be adopted more quickly in some countries, where registration is currently an important obstacle. More importantly, by allowing more suppliers to participate in national procurement processes, they could make some markets more competitive and reduce prices. The impact will be greatest over the medium term, when developing country manufacturers are expected to enter markets for additional important vaccines, including rotavirus, pneumococcal conjugate, and HPV.
[56] This work is still ongoing and a full assessment of its impact is not yet available. However, preliminary observations show that: i) several countries accepted the WHO prequalification as basis for accelerated registration of vaccines, reducing timelines from over 1 year to a few months; ii) up to present, no country has delayed introduction because of a registration issue; iii) both countries and WHO strengthened their capacities and got accustomed to/improved the expedited procedure, increasing the likelihood of its use in future.
[57] WHO HQ/HIS/EMP/RHT/RSS team.

payment, thereby building supplier confidence and reducing price fluctuations. It has also strengthened domestic commitment to immunization, built regional solidarity, and enhanced bargaining power with suppliers. It has almost certainly played a crucial role in the region's impressive immunization performance, including in the introduction of new vaccines.[58,59]

UNICEF, for its part, offers a range of procurement services to non-GAVI MICs, including: i) Reference pricing in instances where a self-procuring MIC requests UNICEF to negotiate prices on its behalf, e.g. as part of a reference pricing scheme; ii) single-country tendering in instances where a MIC requests specific vaccines for which UNICEF does not have a pre-existing long-term framework agreement or tender against which it can award additional MICs quantities; iii) multi-country tendering (pooled procurement) in instances where volumes from multiple MICs can be pooled and tendered together. UNICEF procures traditional vaccines (e.g. BCG, OPV, DTP, measles, MR) on behalf of a wide range of non-Gavi MICs: in some cases, this demand can be pooled by integrating it into existing tenders. UNICEF has recently procured newer vaccines such as PCV and rota through a pooled MICs tender and IPV for non-Gavi MICs through a separate pooled tender. In both cases, manufacturers have offered tiered pricing mainly based on country income.

UNICEF's MICs tender has not so far been as successful as hoped. Although preliminary analysis suggests several contributing factors, concern over the credibility of the demand that underpin such a tender has emerged as a crucial impediment to greater participation of suppliers. Overcoming this will require greater certainty not only about the timing of vaccine introduction by participating countries, but also about the availability of sustained funding and the timeliness and reliability of payment. An important lesson from this experience is that the benefits of pooled procurement can only be realized if substantial progress can be made in consolidating demand—many of the activities included in the MIC Strategy can contribute to this goal. Similar considerations apply to another recent effort in this area: the attempt by WHO EMRO to create a new regional pooled procurement mechanism.

The Task Force discussed extensively the way forward in this area and agreed: i) to develop and disseminate lessons learnt from current and past procurement initiatives for MICs, including the UNICEF MICs tender and the EMRO pooled procurement initiative; ii) to focus on activities that would contribute to consolidating demand (e.g. harmonization of product choices, expedited product registration, strengthening of country commitment and financing) through a strong collaboration between WHO, UNICEF, and other partners; iii) to explore further the potential of alternative tendering strategies and solutions with deeper engagement of manufacturers, including the possibility of new MICs pooled procurement efforts underpinned by greater demand consolidation; iv) to continue existing procurement services for MICs through the PAHO RF and UNICEF.

Influencing market dynamics

The MIC Task Force also discussed measures to influence vaccine markets as a way of increasing access to timely and affordable supply. All MICs would benefit from lower prices and more secure supply that more competitive vaccine markets could bring, especially for new vaccines currently supplied by only one or two manufacturers. In addition, countries that rely on domestic production might benefit from measures that facilitate development of new vaccines by their producers. There are currently about 12 producing countries among the non-Gavi MICs.[60]

[58] PAHO. "Pan American Health Organization Revolving Fund." Available at: http://www.who.int/immunization/newsroom/PAHO_Revolving_Fun_FINAL.pdf.
[59] Tambini G1, Andrus JK, Fitzsimmons JW, Roses Periago M. (2006): Regional immunization programs as a model for strengthening cooperation among nations. Rev Panam Salud Publica 20:54-9.
[60] Argentina, Brazil, Bulgaria, China, Egypt, Iran, Mexico, Romania, Serbia, Thailand, TFYR of Macedonia, Venezuela (Source: WHO/EMP/RSS/ NRA group, 2014)

Several agencies and organizations are currently working to influence vaccine markets through both demand- and supply-side interventions (particularly to improve the supply base). This work includes negotiations with manufacturers, procurement policy, push and pull incentives for manufacturer investment, and advocacy. Some of the most important initiatives seek to accelerate the entry of emerging manufacturers into markets for important new vaccines. Of note, Gavi is currently working to identify potential options to provide Gavi-graduated countries with access to appropriate prices (the ATAP initiative). This initiative is also looking into possible inclusion of non-Gavi LMICs.

The Task Force acknowledged the considerable work in this area while noting that most of it focuses primarily on the Gavi market. The Task Force also noted that many of the interventions included in the MIC Strategy will influence markets, mainly by consolidating demand. Given this context, the Task Force proposes to make use of existing mechanisms such as the UNICEF and PAHO revolving fund tender processes and to encourage organizations working with manufacturers, including the Bill & Melinda Gates Foundation, to include provisions benefitting non-Gavi MICs in access agreements.

The MIC Strategy

Goal	Enhance sustainable access to vaccines for populations in middle-income countries to meet GVAP targets			
Driving Principles	The MIC Strategy is driven by GVAP principles of country ownership, shared responsibility, integration, sustainability & innovation. In addition, it seeks to: • Address inequities within and among countries • Maximize health impact • Consider technical and political feasibility • Maximize value for money • Complement existing and planned efforts			
Country Scope	All middle-income countries not supported through the Gavi Alliance			
Objective	Raise and sustain equitable immunization coverage & enable new vaccine introductions			
Focus areas	**Strengthened decision making** for timely and evidence-based immunization policy & programmatic choices Through: • Establishing & strengthening NITAGS • Strengthening national capacity to generate evidence for decision-making	**Increased political commitment & financial sustainability** of immunization programmes Through: • Strengthening legislative basis for immunization • Advocating for immunization to achieve set immunization spending targets • Mobilizing national resources and increasing efficiency in resource use	**Enhanced demand for & equitable delivery of immunization services** Through: • Addressing vaccine hesitancy & building community demand • Strengthening in country supply chain & data systems	**Improved access to affordable and timely supply** Through: • Increasing procurement skills and knowledge • Increasing access to revolving funds • Harmonizing product choice & registration processes • Increasing price Information • Strengthening pooled procurement options • Influencing market dynamics
Strategic enablers	Country commitment to and investments in immunization Coordination among international and local partners International and national advocacy & country-to-country peer learning Strong monitoring & evaluation efforts			

The strategy as a whole: implementation and impact

The Task Force believes that the activities outlined here make up a coherent and comprehensive package of assistance to MICs as they strive to meet the GVAP goals. The proposed services and new initiatives address the major needs articulated by MICs and work together to strengthen each step on a path to meeting the goals, from rigorous decision-making through access to affordable supply and sustainable financing to strengthened immunization delivery systems.

The strategy, if successfully implemented, would help countries achieve the GVAP goals and reduce the burden of vaccine-preventable disease through three main causal channels. First, by strengthening immunization decision-making, it would make it more likely that countries consider adding new vaccines to their immunization programmes in a timely fashion and do so where the evidence supports such a choice. Second, by addressing important weaknesses in immunization delivery and combatting vaccine hesitancy, the strategy would help to increase coverage of both new and old vaccines. Third, by enhancing and consolidating MIC vaccine demand while at the same time addressing the supply side of vaccine markets the strategy would give many MICs access to lower vaccine prices. This, and the strategy's advocacy work on domestic financing, would in turn allow some countries for whom cost and financing have been obstacles to introduce important new vaccines. Lower prices for already introduced vaccines would free up resources that could be used for other immunization needs or for other health priorities.

The importance of demand consolidation—and the extent to which many of the activities making up the MIC Strategy could contribute to it—became clear during the Task Force's discussion on pooled procurement. Pooled procurement can be a powerful tool for achieving both lower prices and more secure supply, but its benefits will be limited unless manufacturers can be offered the prospect of predictable demand backed by secure financing and timely payment. Timely and rigorous introduction decisions, sustainable domestic financing, streamlined and aligned processes for vaccine registration, and access to revolving funds when needed are a critical part of the solution. These factors, which are also crucial for countries that choose to self-procure, can work hand-in-hand with other activities to influence vaccine markets, such as access agreements with suppliers and on-going efforts to ease the entry of new suppliers and make key markets more competitive.

Although the strategy addresses many of the most important needs of MICs, it is important to acknowledge what it does not or cannot do. It does not tackle directly the social determinants that underlie disparities in access to immunization as well as other health services. It can help only at the margin where problems in immunization systems and decision-making stem from deep-seated weaknesses in governance and institutional capacity. Perhaps most importantly, although advocacy—for domestic financing, for immunization in general—can play an important role, an international strategy can only do so much to create political will where it is lacking. Finally, the strategy only proposes very limited and catalytic external immunization financing for MICs, mainly for targeted technical assistance. Instead, it relies on building sustainable domestic financing and facilitating lower vaccine prices to help countries pay for needed vaccines.

The MIC Strategy is focused on non-Gavi MICs and is intended to complement Gavi's strategy for its eligible and graduating countries. It does so in three ways. First, it extends important services to and attempts to address critical challenges faced by a group of countries that have never had access to these kinds of assistance through Gavi. Second, it can provide some continuity of support to countries that have graduated from Gavi and thus help to ensure that the investments Gavi has made in these countries are sustained and extended. The details of this transition will depend on choices made by the Gavi Alliance Board this spring, as it reviews its eligibility, graduation, and co-financing policies and a policy to ensure access to affordable prices for graduated countries (ATAP). Third, by helping to strengthen and consolidate demand from non-Gavi MICs, the MIC Strategy can

complement the efforts of Gavi and its partners to influence important vaccine markets and thus assure affordable and sustainable supply for all developing countries.

Twenty-four countries are currently expected to graduate from Gavi support by 2020 and thus enter the ambit of the MIC Strategy within the initial 2016-2020 period.[61] Sixteen of these countries crossed Gavi's eligibility threshold and began the graduation process in 2011, after the eligibility policy was revised; eight more countries have begun graduation since. A further eight countries are currently projected to enter graduation between 2016 and 2020, and thus to lose Gavi support during the second MIC Strategy period, 2021-2025. Some of these countries are very large: Indonesia began graduation in 2011, Nigeria entered this this year; India and Pakistan are among the countries expected to graduate before 2025. The entry of these countries will thus have profound implications for the MIC Strategy and it is important to analyse the extent to which the proposed activities will address their needs or if changes to the Strategy would be required.

In general, the current set of graduating countries, most of which are projected to have introduced five or more new vaccines from Gavi portfolio by the time they graduate, are in a good position to sustain the gains achieved with Gavi support. In many respects, the needs of the graduating countries are similar to those of the current non-Gavi MICs: some need help with self-procurement or with removing obstacles to continued procurement through UNICEF; although most have established NITAGs, some would benefit from further help in strengthening decision-making; many have weak regulatory agencies. The MIC Strategy is well positioned to help in these areas. Although most of the current graduating countries have quite high immunization coverage, 9 of 24 had DTP3 coverage below 90% in 2013 and four—Nigeria, Indonesia, Congo, and Ukraine had coverage persistently below 80%. The strategy's measures to address vaccine hesitancy and strengthen selected aspects of immunization systems can help, but probably cannot by themselves remedy these more deep-seated deficiencies in immunization performance. Finally, analyses carried about by the Gavi Secretariat as part of the current review of graduation policy show that a subset of graduating countries face a serious challenge in rapidly scaling up domestic spending to pay for large vaccine portfolios as Gavi support is withdrawn. This is a challenge unique to this subset of Gavi graduates, which the MIC Strategy can do little to ease in the short run. Approaches to mitigating the fiscal risk facing some graduating countries will be considered by the Gavi Board in June.

The MIC Strategy should reflect the characteristics of the countries it is intended to serve, particularly their greater capacity and autonomy, but also their heterogeneity. For this reason, the Task Force envisions the strategy as a menu of services from which countries could request assistance, focusing on areas that they themselves identify as priorities. Although the details of implementation remain to be worked out, many of the proposed activities will emphasize collaboration among MICs and peer-to-peer learning as much as technical assistance provided from the centre. To reflect greater capacity and autonomy, countries would also be asked to cover the greatest share in the cost of the strategy: technical assistance, when it is requested, would be subsidized rather than provided for free.

The WHO secretariat has estimated the potential cost of the various components of the strategy, working from information provided by agencies currently involved in similar activities. These estimates must be considered preliminary, as the actual cost will depend on country demand for these services, but the total annual cost of implementing the package described here is expected be about $20 million. This relatively low cost reflects the strategy's focus on targeted technical

[61] Gavi is currently reviewing its eligibility and graduation policies—decisions taking by the Gavi Alliance Board in June of 2015 could affect the precise timing of the end of financial support for specific countries, as well as nature of Gavi's engagement with graduated countries.

assistance to remove important obstacles while relying heavily on countries own resources to achieve their immunization goals.[62]

The Task Force is exploring an innovative approach to increasing the credibility and market impact of MICs vaccine funding. This mechanism, which could involve a development bank, would be based primarily on the budget commitments of participating countries and would thus depend critically on country commitment.

The potential impact of the MIC Strategy, if fully implemented, is difficult to estimate, as the strategy would not directly provide vaccines or immunization services but act to remove obstacles to higher immunization performance. Yet, the Task Force believes that the package of activities in the strategy can contribute to alleviating a substantial fraction of the remaining burden of vaccine-preventable disease in the non-Gavi MICs, which is estimated at about 150,000 deaths per year in 2014, rising to about 530,000 deaths in 2020 if the 24 countries (including Nigeria) expected to lose Gavi support by then are included.[63,64] Even if the strategy were not implemented, countries would continue to improve immunization delivery and introduce new vaccines, albeit more slowly: a simple analysis, using the LiST model and based on linear extrapolation of trends over the last five years, suggests that perhaps 50,000 lives would be saved in current non-Gavi MICs over the initial strategy period (2016-2020) by such a continuation of current rates of improvement, in addition to those saved by 2013 levels of immunization.[65] If all current non-Gavi MICs that have not already done so introduced the pneumococcal conjugate and rotavirus vaccines while increasing coverage of these and the vaccines already in their portfolios to high levels by 2020, as many as 200,000 more deaths could be averted over this five-year period by pneumococcal conjugate, rotavirus, and Hib vaccination alone. A substantial number of additional lives could be saved by introduction of HPV and increased coverage of measles and Hep B vaccines. This estimate can be seen as representing an upper bound on the potential incremental impact of the MIC Strategy. A more modest scenario, in which the recent rates of adoption of the pneumococcal conjugate and rotavirus vaccines are doubled by implementation of the strategy, might prevent 60,000 deaths over current trends.

These estimates are intended only to give a sense of the potential impact of the strategy, if it were broadly implemented and led to substantial improvement in country performance. More precise and country-specific estimate will be possible once countries have prepared specific plans and defined priority areas of work within the strategy.

The Task Force envisions that the impact of the strategy would be monitored through existing GVAP channels, using the already agreed targets and indicators. A grant oversight mechanism could be established to monitor implementation of the strategy and provision of assistance to countries.

[62] The already planned resource mobilization for VII is not included in the preliminary estimate of incremental costs for the MIC Strategy. Combined with estimated potential impact, the proposed funding investment will be evaluated for its cost effectiveness.

[63] Estimates for the baseline year are based on WHO CHERG data for deaths from diarrhoea, measles, meningitis, and pneumonia. Estimates for 2020 assume that vaccine-preventable deaths grow in proportion to birth cohorts. It should be kept in mind that currently available vaccines can prevent only some of these deaths even at high coverage, as they provide protection against only some strains or serotypes of some of the pathogens that can cause these illnesses and, especially in the case of the rotavirus vaccine, are not 100% effective.

[64] The Task Force has also analysed data from the TRIVAC model on vaccine-preventable morbidity in non-Gavi MICs, but at this time estimates are available only for pneumococcal disease.

[65] This and the other impact estimates presented in this paragraph are derived by applying estimates of lives saved per 1000 children vaccinated in Gavi countries (L.A. Lee et al (2013). The estimated mortality impact of vaccinations forecast to be administered during 2011–2020 in 73 countries supported by the GAVI Alliance. Vaccine 31S:B61-B72), adjusting for the difference in average under-five mortality between Gavi countries and the current non-Gavi MICs, and applying these adjusted rates to projected numbers of people immunised with pneumo, rota, and Hib in the three scenarios. These impact numbers are similar to estimates derived from an independent LiST analysis of vaccine impact in the non-Gavi MICs carried out by Results for Development for the Task Force.

Next steps

The MIC Task Force is submitting its strategy for discussion at SAGE in April 2015. The proposed strategy will then be fine-tuned to reflect SAGE feedback as well as continued consultation with regions, countries, and participating agencies. The Task Force will also need to begin concrete discussions with potential donors to ascertain their interest in supporting these efforts. Depending on the outcome of these discussions, the Task Force will then move to defining how the strategy would be implemented: how countries would request assistance, how countries and partner organizations would work together, how donor funds would be managed, and how the various activities and participating organizations would be monitored, and evaluated. The implementation plan should also define a clear exit strategy, a timetable or set of criteria for ending support to countries. The Task Force recognizes the opportunity that the MIC Strategy offers for innovation in the way its participating organizations work with each other and with countries.

Annex I: Membership of the MIC Task Force

1. AMP	• Alex Adjagba, Director SIVAC Initiative • Jean-Bernard Legargasson, Program Leader , Health Economics and Medical Anthropology
2. BMGF	• John Yang - Senior program officer, Vaccine Delivery • Greg Widmyer - Deputy director, Vaccine Delivery
3. Gavi Secretariat	• Aurelia Nguyen – Director, Policy & Performance • Santiago Cornjeo – Senior Specialist
4. Sabin	• Mike McQuestion - Director, Sustainable Immunization Financing • John Andrus, - Executive Vice President
5. Task Force for Global Health	• Alan R. Hinman - Director for Programs, Center for Vaccine Equity
6. UNICEF PD	• Gian Gandhi - Senior Health Specialist (Policy & Partnerships), Immunization Unit, Health Section
7. UNICEF SD	• Heather Deehan - Chief of the Vaccine Centre
8. WHO HQ (Chair) and Regional Offices	• Michel Zaffran - Coordinator, EPI, FWC/IVB • Tania Cernuschi - Technical Officer, Vaccine Pricing, Supply, Procurement, FWC/IVB/EPI • Niyazi Cakmak - EURO - Technical Officer, Communicable Diseases, EU/RGO/DCE/VPR/VPI • Cuauhtemoc Ruiz-Matus - Regional Adviser AMRO • Daniel Rodriguez - Advisor, Revolving Fund Management, AMRO/FGL/IM • Nadia Teleb- Regional Adviser, EMRO • Peter Beyer, Senior Advisor, HQ/HIS/EMP/PHI
9. World Bank	• Karima Saleh – Senior Health Economist, Health, Nutrition & Population

Annex II: Main information sources for assessment of needs and mapping of current activities

- Literature review, including as main sources a Synthesis Report of New Vaccine Adoption in Low-Middle Income Countries by Results for Development (2011); Gavi graduation assessments and LMIC assessments done as part Gavi's ATAP work; WHO/UNICEF Effective Vaccine Management country reports; and peer-reviewed articles.[66] These sources included studies of the following countries: Albania, Angola, Armenia, Azerbaijan, Bhutan, Bolivia, Cabo Verde, China, Cote d'Ivoire, Ecuador, Egypt, Georgia, Ghana, Guyana, Honduras, Indonesia, Kiribati, Kosovo, Lao PDR, Lesotho, Micronesia, Moldova, Mongolia, Morocco, Nigeria, Panama, Papua New Guinea, Philippines, Rep. Congo, Samoa, Sao Tome and Principe, South Africa, Sri Lanka, Sudan, Swaziland, Syria, Thailand, Timor-Leste, Tunisia, Turkey, Ukraine, Uzbekistan, Vanuatu, Vietnam, West Bank and Gaza, Zambia.

- A survey of needs and current support activities in the following countries: Morocco, Jordan, Egypt, Libya, Palestine, Iran, Iraq, Lebanon, Syria, Tunisia, Albania, Belarus, Kazakhstan, Hungary, Bulgaria, Serbia, Bosnia & Herzegovina (Federation and Republic).

- An in depth analysis of eight geographically diverse "sentinel" countries: non-Gavi or Gavi-graduating MICs with either a high absolute burden or a high rate of vaccine-preventable disease and, in some cases, other special characteristics: Philippines, Egypt, Cape Verde, South Africa, Thailand, Ecuador, Indonesia, and Angola.[67]

- Finally, this work was vetted through consultations with the European and Eastern Mediterranean WHO regional offices and their member countries and bilateral discussions with several partners.[68]

- Survey and interviews with the following agencies: Agence de Médecine Préventive (AMP), Bill & Melinda Gates Foundation (BMGF), Clinton Health Access Initiative (CHAI), Gavi, Harvard Global Health Institute, Johns Hopkins University International Vaccine Access Center (IVAC), Médecins Sans Frontières (MSF), National Institute for Health and Care Excellence (NICE) International, Sabin Vaccine Institute, Task Force for Global Health (TFGH), UNICEF Programme & Supply Division, United States Agency for International Development (USAID), World Bank, WHO headquarters, and the following WHO regional offices: the Eastern Mediterranean Region (EMRO), the European Region (EURO), the Pan American Health Organization (PAHO), the South-East Asia Region (SEARO), and the Western Pacific Region (WPRO).

[66] R4D's report is available at http://www.who.int/immunization/programmes_systems/financing/analyses/Obstacles_to_New_Vaccine_Adoption_in_LMICs.pdf).
[67] Analysis is available upon request.
[68] Detailed results of these assessments are available upon request.

Annex III: Mapping of ongoing support activities in MICs

One of the mandates of the MIC Task Force was to conduct a mapping of support activities by immunization partners targeting MICs. The mapping has two main goals: to understand the level of engagement of partners in MICs and to highlight how these activities could better respond to the needs of MICs. Activities are therefore colour coded according to the below categories:

- The activity is "sufficient, to be continued": the activity is working well and is likely to achieve impact if continued. Activities that have just been started are also classified in this category.
- The activity "could be expanded /strengthened": the activity is working well and could be continued, but it probably requires support to strengthen and/or expand actions to achieve greater impact in MICs.
- The activity "requires modifications": the activity as-is is not likely to yield sufficient results and might require some changes and adjustments to achieve greater impact in MICs.
- "Not applicable, not enough information": the classification is not applicable or there is not sufficient information to classify the activity.

Contents

Sufficient, to be continued | Could be expanded/strengthened | Requires modifications | Not applicable, not enough information

1. Strengthened decision making

Establishing & strengthening NITAGS

Form of assistance	Org.	Activity name & Description	Countries covered	Challenges & limitations	Successes & development	Collaboration
TA, Financing, Training	AMP	**SIVAC** - Support countries to set up or strengthen NITAGs (activities include in-country TA and training, promotion of NITAG collaboration and a resource centre for knowledge sharing)	19 LICs & MICs	- Support limited to Gavi countries, with limited funding outside of Gavi countries -Challenges: need solid institutional integration to guarantee financial sustainability and resistance to political turmoil ; scarcity of HR in secretariats & lack of national experts More info on challenges & successes on: http://www.sciencedirect.com/science/article/pii/S0264410X14016697	- In several countries, new NITAGs have impacted on recent vaccine decisions - Developed countries reported a positive impact from SIVAC activities - There is demand from countries - Resource centre for knowledge sharing - Activities could be extended to other non-Gavi countries	WHO HQ, WHO Regions, BMGF, PAHO, WAHO, Sabin, CDC, existing NITAGs
Technical and management assistance, Advocacy	CHAI	**New Vaccine Introduction (NVI):** - Evidence-based NVI decision-making for antigen prioritization - Strengthening government working groups - Data analysis support (sometimes also including assessment and support in improving data collection mechanism)	MICs: Nigeria, Cameroon, Vietnam, India		- Depending on funding availability, impact, priorities and other considerations, CHAI may consider supporting MICs where CHAI has a country office, but no existing vaccine programs.	
TA, Training	NICE	**International Decision Support Initiative (iDSI) :** - Build capacity in the generation of evidence about the cost effectiveness of technologies and the use of evidence in health policy - Currently in pilot phase (Philippines)	LICs & MICs	- Not vaccine-specific - Lack of locally-generated evidence - Lack of institutional processes to consider evidence in a transparent and accountable manner - Currently in development and difficult to assess impact on MICs and on immunization	- The network is growing, so iDSI will have capacity to increase current work in country or engage in new initiatives, where activities align with the remit and objectives of IDSI. - Still gathering ideas, eg. idea of floating hubs that share expertise in particular regions	HITAP, BMGF, DFID, Rockefeller Foundation, World Bank
TA, Capacity building	WHO & Gavi	**Gavi graduation assessments** - Conducted by Gavi (Secretariat and Alliance partners) to develop plans for successful country graduations - Include analysis of NITAG performance - Technical assistance available through Alliance partners during the plan implementation phase	Gavi-graduating countries	- Limited to Gavi-graduating countries. - To date (Mar 2015), mostly conducted in countries close to graduation (5 out of 11 assessments conducted in countries graduating in 2015/16), with reduced time available for making programme adjustments	Partner wide effort for a comprehensive approach to graduation	AMP
Advocacy, TA, Meetings, Training, Financing, Cooperation	WHO (regions)	- Sub-regional NITAG (eg. RTAG in EURO (ETAGE)) - Normative guidance on establishment and strengthening of NITAGs - Support on vaccine related legislations (support provided through SIVAC, a WHO collaborating centre)	All countries	In principle available to all countries, but limited resources to proactively engage with non Gavi countries (HR and financial)	- Role of NITAG particularly relevant in self-procuring MICs	NITAGs, Regional TAGs, CDC

Sufficient, to be continued | Could be expanded/strengthened | Requires modifications | Not applicable, not enough information

Generating evidence for decision-making

Form of assistance	Org.	Activity name & Description	Countries covered	Challenges & limitations	Successes & development	Collaboration
TA	AMP	- Analysis of costing and financing of routine immunization and NUVI - Sentinel site disease surveillance for clinical and lab confirmed cholera (Africhol) - Use of economic evaluations for decision-making (training)	Ghana, Cameroon, Cote d'Ivoire, Nigeria, South Africa	- Decision making tools and scientific evidence often limited (eg. BoD)	Working with tools that go beyond the simple CEA analysis (eg BoD, affordability analyses, budget impact analyses …)	
Financing	BMGF, IHME	**The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD)** - Produces annual updates to critical information and data such as the effects of different diseases that kill people prematurely and cause ill health, comprehensive estimates of the disease burden attributable to different risk factors and changing disease patterns	All countries	- Data related to vaccines is limited	Large and detailed scientific effort to quantify levels and trends in health	
Financing, Tool development, Data collection & dissemination	BMGF	**Portfolio of studies** - Large portfolio of studies in epidemiology, etiology and burden of disease targeting vaccine-preventable diseases	Various MICs in several regions	- No public access to the repository		Several partners
Tool development,	Gavi	**Disease dashboard** - Using empirical evidence to measure the impact of vaccination in Gavi-supported countries	Gavi-countries	- Not created yet, being developed		WHO
TA, Training, Financing, Advocacy, Meetings, Analyses	JHU IVAC	- Data for decision-making: supporting NITAG data needs for PCV and RV, synthesize data, cost of illness studies, etc. - Policies and recommendations: policy surveys, advocacy support on IPV in MICs - Global disease burden on PCV, Hib, Mening. and RV: data synthesis for RV ; TA, funding, and training for global disease burden [data collection] for PCV, Hib, meningitis ; Pneumonia etiology studies in 7 countries (incl. South Africa, Thailand, Zambia)	Data for decision-making: India, Nigeria, others as requested. BoD: work in about 13 MICs	- Limited number of countries		
Tool development, TA, Training, Advocacy	PAHO	**ProVac & ProVac International Working Group (ProVac IWG)** - To strengthen economic analyses leading to informed decision-making on introduction of new and underutilized vaccines - Key activities include: Economic evaluation & evidence (costs, benefits, cost-effectiveness; Tools & methodologies; Technical assistance and training	7 countries outside of PAHO (ProVac IWG)	- Outside of PAHO, the use of ProVac is limited to 7 countries and 3 regions (AFR, EMR, EUR) - Funding is limited	- 33 studies completed in 22 countries - Country-led effort, strong country-ownership - ProVac could be expanded to other countries with additional funding	AMP, Sabin, PATH, CDC, WHO, BMGF
TA, Financing	TFGH	- Burden of influenza - Introduction of influenza immunization for high risk groups, especially pregnant women	Laos, Nicaragua, Armenia, Morocco	- Limited to influenza - Limited to 4 MICs	- Expansion to an additional 2-8 countries over the next few years (number dependent on funding)	CDC, BMGF
TA, Financing,	WHO (regions)	**Disease burden** - Synthesis of all available published and unpublished (eg. on JE) disease burden studies, Hepatitis B serosurveys, Hepatitis B birth dose assessment - Assessment of BoD for new vaccines to be introduced - Assess population immunity (eg. MR), conduct EPI & VPD surveillance reviews	Some countries of the regions	- Some activities limited to Gavi-countries - Limited funding and resources for regional or country studies which are often requested as evidence for decision making	- Need further resources to increase scope of activities and channel TA to countries	
Guidelines, Tool development, TA, Coordination	WHO	**Cost analyses and the broader economic impact of vaccination** - Assess the broader economic impact of vaccination: value-added of the vaccine and its economic, social, fiscal etc. impact for the country - Provides evidence for decision-making to get vaccines on the agenda: CEA, CE analysis, tools (eg. TRIVAC and C4P for HPV) - TA on cost-effectiveness analysis for new vaccines.: e.g. Vaccine effectiveness studies, Vaccine impact assessment studies, Regional network for Surveillance of diseases	All countries	- Lack of data and evidence - Funding is limited - Some tools are used in Gavi-countries only (even though available to all, eg. C4P)	- Particularly relevant to MICs - The area needs further research - WHO is equipped with technical skills and mandate to increase range of TA to non-Gavi MICs, but requires additional resources (HR and financial)	AMP
Guidelines, TA	WHO (HQ)	Policies recommendations: eg. vaccine introduction guidelines and tools, recommendations for routine immunization, multidose vial policy, vaccine position papers, evidence generation on disease burden, optimizing delivery schedules	All countries		- Used to inform decision-making - Publicly available online	

Sufficient, to be continued | Could be expanded/strengthened | Requires modifications | Not applicable, not enough information

2. Increased political commitment & financial sustainability

Strengthening national immunization financing, resource mobilization and programme efficiency

Form of assistance	Org.	Activity name & Description	Countries covered	Challenges & limitations	Successes & development	Collaboration
TA, evaluation	AMP	- Analysis of costing and financing of routine immunization and NUVI - In-country and remote technical support to cMYP costing tools	Gavi West African countries	Limited number of countries	Similar approaches could inform spending on immunization and improve costing of immunization in target countries	BMGF, WHO, Gavi
Analyses, Advocacy, Training	JHU IVAC	**Decade of Vaccines Economics (DOVE)** analyses - Advocacy for financing, parliamentarian forums (India, Pakistan), briefings, landscape analysis - Dengue vaccine financing workshops	About 13 MICs	Limited number of countries	*No information on need or possibility to strengthen/expand activity*	
Advocacy, TA, Training	Sabin	**Sustainable Immunization Financing (SIF)** - Support to collective action by public sector counterparts within and across countries to increase budget transparency and accountability, develop sustainable financing mechanisms for immunization and enact legislation assuring public financing for immunization - Done through national and subnational briefings, advocacy events, peer exchanges between countries, costing studies and other participatory action research activities	22 Gavi-countries	- To date limited to Gavi-eligible countries - Challenges: limited fiscal space; chronic dependency on external funding; opacity about health spending; difficulties to change pubic financial management practices; difficulties to measure actual immunization costs and set budget benchmarks (immunizations and other basic services delivered in integrated fashion); lack of knowledge on future vaccine costs	- Increased budget transparency in 11/22 SIF countries to date - Immunization legislation under active development or passed in 19/22 SIF countries - There is increased demand from countries - Expanding to other countries (incl. non-Gavi MICs) - Promotes country ownership	BMGF, Gavi
TA, Financing	TFGH	Support for funding of maternal influenza immunization	Laos, Nicaragua	- Limited to influenza - Limited to 2 MICs	Expansion to an additional 2-8 countries over the next few years (number dependent on funding)	CDC, BMGF
Technical & Management Assistance, Financing	WHO & Gavi	**Gavi graduation assessments** - Conducted by Alliance partners to develop plans for successful country graduations - Include ensuring sufficient scale up of national immunization financing - Technical assistance available through Alliance partners during the plan implementation phase	Gavi-graduating countries	- Limited to Gavi-graduating countries. - Up to present (Mar 2015), mostly conducted in countries close to graduation (5 out of 11 assessments conducted in countries graduating in 2015/16), reducing time available for programme adjustments	Partner wide effort, comprehensive approach to graduation	UNICEF, Sabin, CHAI, WB (since 2015), several partners
Training	WHO EURO	- Training on resource mobilization to improve national capacities: development of a toolkit and training programme - Training on improving programme efficiency - Developing normative guidance	MICs in the region	Limited funding	Normative guidance developed by the region may be used by other regions after adaptation to regional context	
TA, Training, Advocacy	WHO	**Comprehensive Multi-year Plans (cMYPs), advocacy and TA** Technical assistance for preparation of multiyear plans for immunization including costing and planning of financial needs WHO regions: advocacy for allocating more government resources of EPI, capacity building to improve financial sustainability of the programmes, fiscal space analyses, immunization programme costing studies, support on financial management for immunization: health accounts	All countries	- Theoretically available to all MICs, but main demand comes from Gavi-countries (this is a Gavi-requirement) - Limited funding available to non-Gavi MICs	Would be a useful tool to have for MICs	Gavi, AMP, CHAI, several partners
TA, Coordination, Meetings, Analyses	World Bank	- Economic and financial analyses, including allocative efficiency analyses, technical efficiency analyses, Public Expenditure Tracking Surveys (PETS)	All MICs eligible for support	- Not vaccine-specific - The Bank is not sector specific, so loans or grants to immunization would have to be linked to the broader country plan.		

Sufficient, to be continued | Could be expanded/strengthened | Requires modifications | Not applicable, not enough information

Catalytic funding for NUVI

Form of assistance	Org.	Activity name & Description	Countries covered	Challenges & limitations	Successes & development	Collaboration
Financing, TA	WHO (HQ)	**IPV introduction** - Catalytic support for IPV introduction for non-Gavi MICs - Funding for start-up costs - 12 months catalytic procurement	Selected countries	- Limited to the identified countries - Activity in progress and long-term impact is not yet known	- Exceptional, unprecedented support dedicated to some MICs (16) to meet Endgame timelines - Enabled to speed up introduction of IPV	GPEI, TFGH
Financing, Technical and management assistance	World Bank	**Innovative financing** - eg. the AMC and IFFIm - Has historically been a convener and facilitator for discussions on innovative financing instruments for immunization - In 2015 the Bank will convene a group of stakeholders to explore new innovative financing solutions, purchasing solutions and market shaping models to increase sustainably financed access to vaccines in the short to medium term	Mainly Gavi-countries	So far limited to Gavi-countries	New ideas for innovative financing could be explored in the future (incl. bridge funding)	Gavi

Sufficient, to be continued | Could be expanded/strengthened | Requires modifications | Not applicable, not enough information

Emergency funding

Form of assistance	Org.	Activity name & Description	Countries covered	Challenges & limitations	Successes & development	Collaboration
Funding	BMGF	$24.8 M to UN agencies for Ebola response	West Africa	Exclusive focus on outbreaks and acute crisis relief		UN agencies
TA, Training	CDC	**Emergency Response and Recovery Branch** provides technical support for rapid assessment and surveillance, develops planning resources and technical guidelines, and training to strengthen HRH capacity	Bosnia and Herzegovina, Colombia, El Salvador, Iraq, Jordan, Marshall Islands, Micronesia, Palau, Samoa, Swaziland	Not vaccine-specific	Could expand capacity-building efforts to include immunization in long-term crises	OFDA, UNCHR, UNICEF, WHO, NGOs
Funding, Supplies, Expertise	EU	Emergency funding for outbreak response (€60M since March 2014) and for reinforcing capacity of governments to deliver vital public services (€210M)	All	Focus on outbreak response	Focus on capacity-building could be expanded to include long-term crisis support	MSF, ICRC, UNICEF and WHO
Funding, Advocacy	Gavi	- Flexible funding processes, ceilings, and channels, as well as technical support for affected countries - Access to price for organizations vaccinating in emergency situations: Gavi has encouraged manufacturers to offer their vaccines at the "Gavi price" to organizations vaccinating in emergencies,	Gavi countries, Palestine	- Funding is limited to Gavi-countries - The call on manufacturers has not yet generated positive responses		UNICEF, WHO
Funding	International Committee of the Red Cross	**Disaster Relief Emergency Fund (DREF):** loans or grants that can be authorized and released in 24 hours. Argentina, Bosnia & Herzegovina, Botswana, Bulgaria, China, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Hungary, Kazakhstan, Macedonia, Montenegro, Namibia, Panama, Paraguay, Peru, Philippines, Romania, Seychelles	Many countries (listed on the left)	Exclusive focus on acute crisis relief	- Critical resources for immediate disaster response - Rapid release of funds	
Campaigns, Education, Service delivery	International Relief and Development	**Outreach Services for Iraqi Refugees (OSIR)** **Health Linkages and National Networks (HLNN)** **Health Support to Syrian Refugees in Jordan (HSSR)**	All; strong presence in Syrian refugee camps in Jordan	Involved in corruption scandal in Iraq (Jan 2015)	Supports capacity building	UNHCR
Funding, Campaign coordination, Guidelines	UN	**- OCHA** manages **Central Emergency Response Fund** (CERF), capped at $30 million/crisis (allocated to UN agencies including WHO) and **country-based pooled funds** (e.g. Common Humanitarian Fund in Sudan) **- UNHCR** funds and coordinates emergency vaccination campaigns, with funding and procurement assistance from **UNICEF** (focusing on measles and polio campaigns) **- UNICEF Emergency Programme Fund (EPF):** since 2006, ceiling of $75M / biennium	Several, incl.: Bosnia & Herzegovina, Colombia, Guatemala, Iraq, Jordan, Lebanon, Paraguay, Philippines, Syria	Funding needs at an all-time high, straining existing mechanisms	UNICEF experienced in vaccine procurement could be leveraged to assist integrated refugees access immunization services	WHO
Funding, coordination	USAID	**Office of Foreign Disaster Assistance** provides funding to support immunization campaigns during disasters	All disaster-affected countries	Exclusive focus on campaigns	Provides technical and regional expertise; could be expanded to support RI in long-term crises	UNICEF, WHO
Fundraising, Management and distribution of funds	WHO	- Emergency funds including **African Public Health Emergency Fund** and **South East Asia Regional Health Emergency Fund** - Country offices help to raise funds for immunization of refugees outside camps - Proposal for establishment of emergency fund and global health worker cadre endorsed by Executive Board (Jan 2015)	All		Strong financial and programmatic coordination arm; work with integrated refugees could be expanded	Several partners
Funding	World Bank	**Emergency Primary Health Care Restoration Project:** - To improve access to primary health care services among Lebanese populations impacted by the Syrian crisis - Call for creation of new pandemic emergency facility, Jim Yong Kim (Oct. 2014)	Lebanon	Not for refugees	Addresses impact of refugee crises on host country health systems	

Sufficient, to be continued | Could be expanded/strengthened | Requires modifications | Not applicable, not enough information

3. Enhanced demand for and equitable delivery of immunization services

Addressing vaccine hesitancy & building vaccine community demand

Form of assistance	Org.	Activity name & Description	Countries covered	Challenges & limitations	Successes & development	Collaboration
Tool development, Research	LSHTM	**Vaccine confidence project**: - A global surveillance system to identify and track rumours and misinformation related to immunization - Development of a Vaccine Confidence Index	All countries	In development	In development	BMGF
Diagnostic tools	WHO EURO	- Developed TIP (**Tailoring Immunization Programme**) Toolkit to identify behavioural determinants of vaccination (and barriers) - Sample survey questions to assess the specific determinants of vaccine hesitancy developed by the SAGE working group	All countries in the region	- As a new tool, the TIP needs to be evaluated, validated and possibly modified, in particular in LICs % MICs beyond EUR. Needs to be adapted to be used globally - Requires advocacy for social mobilization - Requires funding for expansion - Requires more research and tools - Sample survey questions remain to be validated, in particular in low- and middle income settings	- Discussions with partners and stakeholders are ongoing to advance the use of the TIP tool/survey question - CDC expressed particular interest in supporting the evaluation and adaption of the TIP tool/survey question	WHO HQ, CDC, UNICEF
Communication	WHO EURO	**Mobile phone app** in 2013 to allow parents to track their child immunization (addresses a consistently reported reason for hesitancy: lack of reminder or recall system)	All MICs in the region	Useful communication tool, though not directly related to vaccine hesitancy	Useful communication tool No information on need or possibility to strengthen and expand activity	
Technical and management assistance	WHO & Gavi	**Gavi graduation assessment missions** Conducted by Alliance partners to develop plans for successful country graduations. Include: developing national immunization communication plan, to address vaccine hesitancy &/or to develop AEFI and risk communication. Technical assistance available through Alliance partners during plan implementation phase	Gavi-graduating countries	- Limited to Gavi-graduating countries. - Up to present (Mar 2015), mostly conducted in countries close to graduation (5 out of 11 assessments conducted in countries graduating in 2015/16), reducing time available for programme adjustments	Partner wide effort for a comprehensive approach to graduation	AMP, UNICEF, several partners
Advocacy	WHO	**World Immunization Week** (WIW) The SAGE Vaccine Hesitancy Working Group concluded that the World Immunization Week, in the scope of WHO, is an opportunity to build positive public dialogue around vaccines and immunization	All countries	- Further support and promotion of WIW is needed, in particular by partners and stakeholders such as civil service organizations - More financial support would be helpful to regional offices	WIW has been established as global brand with positive messaging around vaccines and immunization	WHO HQ, WHO Regions, several partners & stakeholders
Policy, Strategy, Guidance	WHO (HQ)	**SAGE Working Group on Vaccine Hesitancy** - Several documents and papers published by the SAGE working Group on vaccine hesitancy: vaccine hesitancy landscape study, systematic review of determinants of vaccine hesitancy and the mentioned report of the SAGE Working Group on Vaccine Hesitancy which is in the process of being published as a special issue of the journal Vaccine.	All countries	Need to validate tools to assess vaccine hesitancy as well as strategies to address it	- Existence of a definition of vaccine hesitancy - Creation of a matrix on determinants of vaccine hesitancy - Indicators to measure vaccine hesitancy have been tested and now included in JRF - Increased recognition of this issue at the international level	WHO EURO, Vaccine hesitancy Working Group members
Training	WHO	Sub-regional trainings on managing vaccine safety concerns, capacity building, communication strategy (eg. Immunization week) and media training ; Development of e-learning tools on vaccine hesitancy	All countries	Several initiatives are ongoing to develop training modules on vaccine hesitancy. These initiatives need to be aligned	Discussions initiated with WHO HQ, WHO EURO, UNICEF, LSHTM, Public Health Canada, other	WHO EURO, CDC, UNICEF
Research, Implementation, Guidelines	Various	Several initiatives are starting or ongoing in countries and involve a wide range of actors: NVAC Working Group on vaccine hesitancy, China MoH, China CDC, Belize, German Federal Centre for Health Education, NCIRS Australia, Romania NIPH, UK Department of Health, US CDC, Canadian Association for Immunization Research and Evaluation, Canadian Pediatric Society, GPEI, BMGF, Robert Wood Johnson Foundation, Canadian Center for Vaccinology, Harvard University, JHSPH, Ottawa Hospital Research Institute, University of Sydney, University of Washington School of Medicine, VAX Northwest, UNICEF, WHO, WHO EURO, vaccine Industry, ...	All countries	- Few examples of concrete actions relating to vaccine promotion/acceptance exist - Not enough global vaccine reporting or surveillance systems currently measuring demand-side indicators, such as vaccine hesitancy - Efforts are disparate and the issue is complex - Funding is limited. Grants often focus on the supply side of immunization but only a few projects funded to work on demand-side factors (e.g. vaccine acceptance, confidence and hesitancy)	- Many advisory committees and organizations have started to deal with the issue of vaccine hesitancy, including encountering and defining the problem of lack of confidence in vaccines, gathering information on the problem and suggesting potential strategies to deal with this issue.	Several partners

Sufficient, to be continued | Could be expanded/strengthened | Requires modifications | Not applicable, not enough information

Strengthening supply chains

Form of assistance	Org.	Activity name & Description	Countries covered	Challenges & limitations	Successes & development	Collaboration
TA, Training	AMP	- **LOGIVAC**: Supply chain pre-service and in- service trainings (in country or in the LOGIVAC Centre in Benin) - **EPIVAC®:** One-year on-the-job training programme in applied vaccinology and management of immunization systems for district medical officers	Nigeria, Senegal, Cameroon, Cote d'Ivoire, Mauritania	Limited to Francophone sub-Saharan African countries	- Currently being expanded to Anglophone countries (hub in Rwanda) - Could be further expanded	UNICEF, Gavi, WHO
Financing,	Gavi	**Global immunization supply chain strategy** - Focuses most intensively on the country level - Focuses on system redesign, as well as 4 key elements of immunization: supply chain managers, supply chain management & improvement plans, supply chain dashboards, cold chain equipment	Gavi-countries	- Vaccine volume increases over time and stretches existing supply chain capacity - Limited to Gavi-countries		WHO, UNICEF, BMGF
Modelling, Analysis	JHU IVAC	**HERMES** (Highly Extensible Resource for Modelling Event-Driven Supply Chains) analysis. - Immunization system redesign	Vietnam, Thailand, India, Senegal	Limited number of countries	*No information on need or possibility to strengthen/expand activity*	Gavi BMGF
Advocacy, Research	MSF	**Vaccine adaptability & service delivery** - Promoting improvement of vaccine products and improved packaging - Conducting research on thermostability of the Tetanus vaccine (through MSF's research arm, Epicentre); - Conducting in-country epidemiological research (eg. Niger) - Vaccine delivery & immunization campaigns	LICs & MICs	Challenges: there is a need for simplified dosing schedules, heat-stable vaccines, easy to administer (eg. Uniject) ; and there is a need for vaccines that better target epidemiological needs of developing countries		
Tool development, TA	UNICEF SD	**VIVA project (VIsibility for VAccines):** - Link country level stock data with scheduled deliveries in a manner that provides a visual overview of projected stock levels - Identify risks of vaccine stock outs/overstocking well in advance to allow for corrective action	All countries. Test countries: The Philippines and Botswana	- Still being developed - Countries are not necessarily aware of the tool. Activity could benefit from communication, advocacy and TA to countries	- Publicly accessible online. An internet interface for all stakeholders to upload, visualize and comprehend the data easily	
TA, Training, Other	USAID	Cold Chain: In-country TA , capacity building, and training in cold chain & logistics	11 countries	Activities limited to some countries		
Technical and management assistance	WHO & Gavi	**Gavi graduation assessment missions** Conducted by Alliance partners to develop plans for successful graduation. Include: - Capacity strengthening (based on EPI review and EVM) - Improvements in cold chain and logistics as part of strategy to improve immunization coverage - Present LOGIVAC trainings if necessary (AMP) - MLM training identified as priority actions in Graduation plan when relevant	Gavi-graduating countries	- Limited to Gavi-graduating countries. - To date (Mar 2015), mostly conducted in countries close to graduation (5 out of 11 assessments conducted in countries graduating in 2015/16), with reduced time available for making programme adjustments	Partner wide effort for a comprehensive approach to graduation.	AMP, UNICEF, several partners
Technical and management assistance, Financing	WHO & UNICEF	**Immunization Supply Chains & Logistics** - Cold chain logistics planning & management, including normative guidance, support on design of cold chain infrastructure, repair and maintenance, strengthening & improving cold chain capacity, cold chain assessment for new vaccines introduction, sub-regional meetings on strengthening vaccine management, advocacy and TA to priority countries to develop SOPs. - Information system: stock management (eg. VSSM), Cold Chain Equipment (CCE) management, temperature monitoring, web-based cold chain equipment inventories, accelerated adoption of new technologies, data analysis support - Procurement support for cold chain equipment (UNICEF SD, PAHO RF, CHAI)	All countries	Funding is mainly limited to Gavi countries and technical support to non-Gavi MICs is limited		USAID, PATH, CHAI, AMP
Technical guidelines, Advocacy, Monitoring	WHO	**Effective Vaccine Management (EVM) Initiative** - Provide materials and tools needed to monitor and assess vaccine supply chains and help countries to improve their supply chain performance (TA & online) - Technical and financial support for EVM assessment, developing of EVM improvement plans, capacity building and resource mobilization, follow up, re-assessment, etc.	All countries	- Available to all but mainly implemented in Gavi-countries (this is a Gavi requirement) - Implementation in MICs would require additional funding		USAID, PATH, CHAI, AMP
TA, Financing, Analyses	World Bank	**Supply chain strengthening** - Engagement in supply chain strengthening (including working with the private sector) to improve the efficiency and (cost)-effectiveness of supply chains - Best indicators for improved supply chains developed and revised using data from analytic work	All MICs eligible for support	- Not vaccine-specific - The Bank is not sector specific, so loans or grants to immunization would have to be linked to the broader country plan		

Sufficient, to be continued | Could be expanded/strengthened | Requires modifications | Not applicable, not enough information

Strengthening data systems

Form of assistance	Org.	Activity name & Description	Countries covered	Challenges & limitations	Successes & development	Collaboration
TA, Financing	AMP	**African Cholera Surveillance Network: Africhol** - Development of databases and data management tools on cholera disease burden in Africa through a network of surveillance sites (collecting data on demography, symptoms and risk factors in 20 sites in 11 countries) - Forum to share information on activities and develop tools for surveillance sites	11 countries in AFR	- Limited to Cholera - Limited to Africa	Data gathered serves to inform decisions on optimal interventions for cholera prevention and control, including vaccination	BMGF
Financing, Data collection & dissemination	PATH	**Project "Better Immunization Data" (BID)** - Areas of work: national immunization registries, automated report generation, supply chain system tools, use of barcodes, supportive supervision, community micro-training… - Develop immunization management information system components (built upon existing information system tools where they exist) and demonstrate effectiveness and scalability - Identify and extend best practices and create replicable models - Create a learning network of countries	Tanzania, Zambia	Currently limited to 2 countries	- Empower countries to enhance immunization through improved data collection, quality, and use - Expansion and dissemination of tools planned for 2016	BMGF, WHO, WHO AFRO, Gavi, UNICEF, MoH
Technical and management assistance	WHO & Gavi	**Gavi graduation assessment missions** - Conducted by Alliance partners to develop plans for successful country graduations - Include strengthening data management systems and relevant use of data for decision making - Technical assistance available through Alliance partners during plan implementation phase	Gavi-graduating countries	- Limited to Gavi-graduating countries. - To date (Mar 2015), mostly conducted in countries close to graduation (5 out of 11 assessments conducted in countries graduating in 2015/16), with reduced time available for making programme adjustments	Partner wide effort for a comprehensive approach to graduation	AMP, UNICEF, several partners
Coordination, Research, Data collection & dissemination	WHO	**JRF, WHO info repository** - HQ: Data collection and monitoring: Global data collection and dissemination, Global coordination, Research to improve monitoring and evaluation - Regions: support on collection and analysis of EPI/VPD data (JFR)	All countries	There is often more information available for Gavi-countries.		UNICEF
TA, Training, Financing, Surveillance, Tool development, Guidelines	WHO (regions)	**Surveillance networks, data sharing and e-registries, eg:** - Pharmacovigilance: surveillance of Adverse Events Following Immunization (AEFI) - Advocacy and support on implementation of immunization electronic/nominal registries and coordination (eg. PAHO ISIS), establishment of sentinel surveillance systems, surveillance networks, web-based surveillance reporting system, EPI reporting system, HR capacity building, sharing all data collection tools, strengthening capacity of national AEFI committee to conduct causality assessment and foster data sharing	All countries	- Technical support to non-Gavi MICs is limited - Limited knowledge and sharing of best practices regarding the implementation of e-registries - Support could be extended with additional funding - Need to strengthen expertise at country level	E-registries and improved data systems are considered key areas for some regions	
TA, Guidelines, Tool development	WHO (HQ)	**Surveillance & Laboratory capacity** - Measles surveillance; RV surveillance and laboratory networks - Rotavirus and Global Invasive Bacterial Vaccine Preventable Diseases (IB-VPD) surveillance and laboratory networks	All countries	MICs would need financial support to start surveillance (eg. small seed money) and technical support	There is interest and demand from countries	CDC
TA, Guidelines, Coordination	WHO (HQ)	**Information systems** - Norms and standards, guidance on ICTs (including on e-registries), information sharing, coordination - Coverage survey manual and use of home based records - Technical support for software development for selected African countries - Assessing and improving immunization data quality	All countries	- Funding is limited - Implementation and TA for MICs is not foreseen	Still in development	CDC, BMGF, Gavi
Tool development, Communication	WHO (HQ)	**TechNet: online platform** - Practitioner network - Reference library	All countries		Still in development	BMGF
Data collection, Analyses	World Bank	**HealthStats** Data collection and analysis: 2014 Development Indicators/ Development Data Platform/HealthStats	All MICs eligible for support	- Not vaccine-specific - Loans or grants to immunization would have to be linked to broader country plan	*No information on need or possibility to strengthen/expand activity*	

Sufficient, to be continued | Could be expanded/strengthened | Requires modifications | Not applicable, not enough information

4. Improved access to affordable and timely supply

Increasing procurement skills and knowledge

Form of assistance	Org.	Activity name & Description	Countries covered	Challenges & limitations	Successes & development	Collaboration
TA	CHAI	Support for vaccines supply planning and procurement, especially for new vaccines	MICS: Nigeria, Cameroon, Vietnam, India	Limited to 4 Gavi-MICs	- In-country in-depth support - No information on need or possibility to strengthen/expand activity	
Procurement, Coordination, Financing	PAHO RF	**PAHO Revolving Fund** - Component of the TA on immunization in the Region. Pooled Procurement on behalf of Member States in the Americas Region. - Assist countries on demand planning, procurement, regulatory alignment, claim management (e.g. cold chain rupture)	PAHO countries	Only for PAHO Member States	- 41 countries and territories actively participating. - Established 35 years ago	
TA, Training	PAHO RF	**Forecasting** - Capacity building on vaccine and supplies forecasting - Update on vaccine markets to Member States (presentations and reports)	PAHO developing countries	- Limited to PAHO developing countries	With additional funding, PAHO could also support other WHO RO with TA	CDC
Implementation, Tool development	UNICEF SD	**Supply & forecasting** - Follow and present key information on products, including pipeline products. - Publication of market updates with revised supply & demand update per vaccine - Forecast spreadsheet, monitoring - Annual manufacturers consultations	All countries, data on vaccine demand is from UNICEF- procuring countries	- Market updates limited to a few products - Takes only into account demand coming from countries procuring through UNICEF	Raises flags regarding upcoming market shortages	
Technical and management assistance	WHO & Gavi	**Gavi graduation assessments** - Conducted by Alliance partners to develop plans for successful country graduations - Include: TA and identification of bottlenecks; TA on improved procurement systems (Armenia, Azerbaijan, Uzbekistan); capacity building (e.g. international tenders) - Technical assistance available through Alliance partners during the plan implementation phase	Gavi-graduating countries	- Limited to Gavi-graduating countries. - Limited availability of procurement expertise to advise countries during missions	- Partner wide effort for a comprehensive approach to graduation - TA initiatives are considered important and to be continued	Gavi, UNICEF SD, several partners
Technical Assistance	UNICEF & WHO	**Vaccine Procurement Systems Assessments/Vaccine Security Missions** - Review of vaccine procurement systems, performance evaluation and identification of strengths and weaknesses - Orient countries on the changing vaccine market and support them in the development of accurate forecasting and timely and reliable funding	All countries	Limited to ad hoc missions, based on specific country request	- Provides recommendations for strengthening the vaccine procurement system	
TA, Financing, Analyses	World Bank	**Public procurement reform**: reviews the procurement legislative environment, institutional capacity, identifies bottlenecks and provides technical assistance in best practice examples.	All countries	- Not vaccine-specific - The Bank is not sector specific, so loans or grants to immunization would have to be linked to the broader country plan.		
TA, Training, Meeting	WHO (regions)	- TA on forecasting, harmonizing product/registration requirements and procurement legislation - Collaborating with UNICEF SD on procurement of vaccines for MICs - Capacity building on improving efficiency of procurement - Enhance capacity of MIC to procure vaccine through ICB (international competitive bidding) and local procurement - Idea of regional workshops (on procurement, vaccine security) being explored and developed	All countries	- Procurement rules and practices can prevent procurement options (e.g. national regulations conflicting with UNICEF's rules) - Technical support to non-Gavi MICs is limited - No dedicated funding or support mechanism for non-Gavi MICs for providing technical assistance	- Procurement through UNICEF needs to be further explored for some countries - Need more in-country TA - No workshop confirmed yet	UNICEF SD
Other	WHO (HQ)	Facilitate dialogue on supply availability	All countries	- Ad hoc-support, disease-specific - Challenges: Information and analyses on demand & supply forecasting are limited		

Sufficient, to be continued | Could be expanded/strengthened | Requires modifications | Not applicable, not enough information

Increasing access to revolving funds

Form of assistance	Org.	Activity name & Description	Countries covered	Challenges & limitations	Successes & development	Collaboration
TA	JHU IVAC	**Basket Fund** Documentation and technical support on basket funds in Lagos State	Nigeria: Lagos state	Very limited in scope	Looking to work more on an innovative financing mechanism in Asia.	
Technical and management assistance, Coordination, Procurement	PAHO RF	**PAHO Revolving Fund** - Established in 1979, the Revolving Fund (RF) offers a credit line to countries (60 days) - The RF acts as a line of credit, allowing governments to pay for vaccines after receipt of the order - Facilitate the use of local currency for the reimbursement of invoices (almost all countries already prepay or reimbursed the revolving fund in US$) - RF working capital has grown significantly over the years through increased volumes of vaccine purchases and the compounding effect of a 3% service fee applied to each order - In 2014, the RF had a purchase value of $575 M and a capital fund of $130 million	PAHO countries	Limited to PAHO countries	- It is atypical to see countries with default payments - With today's capitalization level and projected purchases using the credit line, every participating country/territory has access to maximum US10 millions of credit - Most countries (36) place 100% of orders using the credit (revolving fund), and the rest use a mix (pre-payment and credit) - Currently, no extra capitalization is needed to cover expected purchases by credit in the next 2 years, at least	
Implementation, Financing, Tool development	UNICEF SD	**Vaccine Independence Initiative (VII)** - Revolving fund that acts as a line of credit, allowing governments to pay for vaccines after receipt of the order - Funds are used by UNICEF to purchase vaccines directly from the manufacturers. The revolving fund is then reimbursed when governments pay UNICEF for the vaccine order (generally 60-75 days following product delivery)	All countries with whom UNICEF has a programme of work may apply. Current use: 13 Pacific Island countries, Kenya, Niger, Capo Verde, Chad. Lao PDR and Nigeria currently evaluating at the ministerial level. In 2014, quite a number of countries 'graduated' from use and are now procuring through standard procurement services	- Countries are often not aware that they can access this support - Need fundraising to raise capital base	- Particularly helpful to countries with issues with access to hard currency, cash flows and high vaccine prices due to high transportation costs and small demand. Has been used for countries to also service their co-financing requirements. - 1 default in 24 years which was subsequently remedied - In February 2015, UNICEF Executive Board has approved extension and expansion of allowable capital base from $10 million to $100 million, subject to available specific-contributions	

Sufficient, to be continued | Could be expanded/strengthened | Requires modifications | Not applicable, not enough information

Harmonizing product choice & aligning registration processes

Form of assistance	Org.	Activity name & Description	Countries covered	Challenges & limitations	Successes & development	Collaboration
TA, Assessment	AMP, WHO	**NRA financial assessment** Project launched by WHO. Objectives: Estimate the costs of vaccine regulation for national medical authorities in target countries; Identify appropriate fee systems in the regulation of vaccines; Improve the financial sustainability of national medical authorities. Timeline: 2013 - 2017	China, India, Indonesia	Currently in 1st phase of the project. Impact is unknown	Will potentially cover 16 developing and developed countries worldwide	WHO country offices, NRAs
Financing	WHO, IVI, Sabin, JHU, IVAC	**Dengue Vaccine Initiative (DVI)** - Key activities related to NRA include technical assistance, training, convening of NRAs (through the support of WHO, to endemic countries that expressed interest in evaluating and licensing the candidate dengue vaccines) - DVI was established to enable the policy environment and country readiness for accelerated introduction of dengue vaccines in endemic countries	Brazil, Thailand, Malaysia, Columbia, Mexico, Vietnam, Indonesia, Philippines	Limited to dengue		BMGF
TA, Training, Coordination, Guidelines	Global and Regional Regulatory Networks	**AVAREF and DCVRN** AVAREF: regional network of regulators and ethicists aimed at strengthening in-country capacity for the regulation of clinical trials including ethical approval. Focuses on development of procedures and protocols for the review of clinical trial applications and evaluation. Such procedures are aligned and adopted in all countries of the network. It also focuses on organizing joint reviews of clinical trial applications and eventually to review marketing authorization applications DCVRN: global network of MICs with fairly developed regulatory capacity. They collaborate among members to discuss concerns and difficulties faced for the evaluation of marketing authorization applications for novel vaccines (eg. Dengue). In collaboration with DVI, an international consultation will be organized for information sharing in the context of registration of dengue vaccines. DCVRN members are working on the development of points to consider documenting the rationale/ lack of rationale to require local clinical trials for the registration or evaluation of variations of imported vaccines. Such points to consider may be included as an annex in the revised version of the WHO clinical guidelines planned to be updated in 2015	- AVAREF: impacts at regional level in 20 countries - DCVRN impacts all countries	Requirements of local clinical trials is more a political issue than technical, the availability of points to consider will provide a framework on the rationale for such requirements but will not ensure the change in policy in individual countries Lack of funding for DCVRN	These initiatives represent effective mechanisms to facilitate the regulatory processes	WHO HQ , AFRO and NRAs
Training, Guidelines	WHO	**Global Learning Opportunities** - Course on regulatory framework for clinical trials - Course on non-clinical and quality evaluation of data for marketing authorization Based on the outcome of the regulatory framework surveys and the guidance document produced, a course for implementation of such guidance will be developed on regulatory framework for registration of medicines		Lack of funding	Could also address best procedural practices in registration	WHO, RO
TA, Coordination, Assessment	WHO	**Facilitating registration of IPV vaccines** Joint reviews were conducted in SEARO and AFRO using the collaborative procedure proposed by WHO for registration of prequalified vaccines under the leadership of the vaccines assessment group in PQT. In EMRO WHO/RSS offered to conduct a joint review of the CTD dossiers required by countries that follow a full review procedure for registration of vaccines independently of whether they are prequalified or not	Selected countries in AFR, SEAR and EMR	- Joint review of registration files necessary but not sufficient to ensure timely registration of vaccines - Additional disharmonized requirements and complicated procedures may impact actual timeframe for registration	- Joint reviews are a successful mechanism to provide technical support and increase capacity in countries - No information on need or possibility to strengthen/expand activity	WHO and NRAs

Sufficient, to be continued | Could be expanded/strengthened | Requires modifications | Not applicable, not enough information

TA, Training, Coordination, Guidelines	WHO (HQ & AFRO)	**GMRH & AMRH** Global Medicines Regulatory Harmonization (GMRH) initiative and the African Medicines Regulatory Harmonization Programme (AMRH): - Supports regional coordination and capacity building for medicines regulatory harmonization - Includes development of harmonized protocols for medicines registration, institutional development and strengthening of National Medicines Regulatory Authorities to improve medicine registration efficiency and transparency, and improve quality management systems	Countries in AFR	- Limited to AFR - Complicated area of work	Would increase access, availability and affordability -No information on need or possibility to strengthen/expand activity	BMGF,World Bank, Nepad, DFID, National Regulators
Research, Guidelines	WHO-(HQ)	**Facilitating regulatory pathways** - Internet search and survey on marketing authorization regulations in HIC , MIC and LMIC to assess requirements regarding registration of emergency vaccines (fast track provisions), requirements for local clinical trials for the registration/variation approvals of imported vaccines, provisions for acceptance of expedited registration procedure for prequalified imported vaccines - Work with manufacturers to assess constraints for registration and management of variations in countries using their vaccines Outcome of this work will support the development of guidance documents on model regulatory frameworks that would include provisions for reliance on other NRAs, for rapid registration of emergency products, reliance on WHO in the case of prequalified vaccines, etc.	HICs, MICs,LMICs	Will not provide information on actual administrative procedures followed in countries	- Seek understanding of major bottlenecks and differences between countries to devise interventions - No information on need or possibility to strengthen/expand activity	WHO, NRAs, RO and manufacturers
Guidelines Training	WHO (HQ)	**Norms and standards** - Development and establishment (through the ECBS) of global technical specifications on the quality, safety and efficacy of vaccines - Development and establishment (through the ECBS) of global reference preparations to support regional or national standards activities - Implementation workshops to help align regulatory requirements and to help build capacity of both NRAs and manufacturers	All countries	Insufficient resources to meet demands	WHO standards used by NRAs and used to define technical basis of PQ process. The greater the implementation, the greater the alignment of regulatory requirements	NRAs
Coordination, Guidelines	WHO (HQ)	**Vaccine Prequalification** - Review of general production process and quality control procedures, testing of consistency of lots, site auditing, and reliance on the NRA responsible for the regulatory oversight of the vaccine - Uses vaccine safety and efficacy data relevant to the target population - Vaccines meet specific programmatic needs, reflected by tender specifications: i.e. VVM type, presentation, labelling, packaging, etc.	All countries	Complicated process that can deter manufacturers to prequalify their products	- Ensures vaccines used in programmes are safe and effective - List of PQ vaccines available online	NRAs
TA, Training, Planning, Monitoring, Fundraising, Guidelines	WHO	**NRA strengthening** - NRA planning workshops - Plan and conduct in-country assessment to develop Institutional Development Plans (IDP), monitor progress - For manufacturing countries: plan and develop road map for vaccine prequalification - Organize trainings by or twinning with well-resourced and functional NRAs with least developed NRAs - Help graduating countries strengthen their NRAs, potentially in preparation for self-procurement or domestic production (Gavi-graduating countries only) - Provide standard methodology and tools - Develop document on Good Regulatory Practices to be later endorsed by ECBS and ECPP	All countries	- Need additional funding and resources at national level - Countries need more technical support	Currently there are 36/43 (84%) functional NRAs in producing countries	Gavi, BMGF, USAID

Sufficient, to be continued | Could be expanded/strengthened | Requires modifications | Not applicable, not enough information

Increasing access to price information

Form of assistance	Org.	Activity name & Description	Countries covered	Challenges & limitations	Successes & development	Collaboration
Technical and management assistance	CHAI	Negotiation support with manufacturers of cold chain equipment and access to price information for antigens and cold chain equipment	MICs: Nigeria, Cameroon, Vietnam, India	- Limited to 4 Gavi-MICs - Challenges: lack of publicly available information; need for more price data per manufacturer and per presentation	*No information on need or possibility to strengthen/expand activity*	
Advocacy	MSF	**The Right Shot & Advocacy work** - Advocacy for price transparency - Providing basic understanding of pricing strategies and detailed information about vaccine product information and prices - Also promoting availability of vaccine price information via marketing & communication (press releases, crowdsourcing, etc.)	All countries, especially MICs	Challenges: Price information is hard to find, making data-comparability difficult ; the vaccine market lacks transparency	2nd edition published in 2015	
Procurement, Communication	PAHO RF	**Vaccine prices** Publication of vaccine prices	PAHO countries	- Price information imited to PAHO developing countries - No volume disclosed - WAP, not real price per manufacturer	- Participation in V3P - Recognized as a contributor to price transparency - Often used as reference prices	
Procurement, Communication	UNICEF SD	**Vaccine prices** Publication of vaccines pricing - UNICEF SD publishes both contract awards and vaccine prices.	All countries, especially Gavi-countries	- Price information mainly limited to Gavi countries - Volumes by manufacturers not disclosed	- Participation in V3P - Recognized as an important contributor to price transparency - Often used as reference prices	
Tool development, Advocacy, Training, Data collection & dissemination	WHO	**V3P: Vaccine Price Product and Procurement** - Providing an online and publicly accessible database of vaccine price information, as well as product, price, and procurement information through an information repository and resource gateway - Price information shared by countries through the online platform or through the JRF - Advocacy through WHO regions and through Gavi graduation assessment missions and plans	All countries, especially MICs	- Limited participation from countries - Complexity of vaccine prices limit quantitative analyses	- 26 countries submitted price info in 2014 - Example of impact: Georgia has successfully used info for price negotiation - New GVAP indicator added: number of countries reporting prices per region as well as a price indicator	BMGF,UNICEF, PAHO, WHO EURO

Sufficient, to be continued | Could be expanded/strengthened | Requires modifications | Not applicable, not enough information

Strengthening pooled procurement options

Form of assistance	Org.	Activity name & Description	Countries covered	Challenges & limitations	Successes & development	Collaboration
Procurement, Coordination	PAHO RF	**PAHO Revolving Fund** - Pooled procurement of vaccines and immunization supplies - Provide countries with: continuous supply, quality products, affordable prices	PAHO countries	Limited to PAHO countries	Successful regional pooled procurement mechanism.	Individual AMR country governments
Procurement, Implementation	UNICEF SD	**MICs New Vaccine Tender** - Issued in Dec 2012. For PCV, Rota and HPV for delivery during the period 2013-2015. - Purpose: accelerate introduction of new vaccines in MICs, expand market of priority new vaccines, and establish reference prices.	All MICs	- Lack of commitment/credible demand from countries - Low participation from manufacturers - Manufacturers ask for non-disclosure of prices	- A handful of countries have or are in the process of introducing PCV, Rota and HPV as a result of the tender [Philippines (PCV, Rota), Albania (PCV), Palestine (PCV), Cook Islands (HPV)] - UNICEF SD is re-evaluating the mechanism	Individual country governments
Procurement	UNICEF SD	**UNICEF Procurement Services** - Aggregating multi-year demand forecasts and pooling procurement of vaccines + devices on behalf of individual countries, development partners and global initiatives. - Handling fees are charged in order to defray the incremental direct and indirect costs that UNICEF incurs by providing services	All countries Gavi-countries (for Gavi-supported vaccines), plus ~20 non-Gavi MICs (mainly for basic/traditional vaccines + devices)	Need communication and procurement TA to countries, maybe through partners (e.g. understand requirements for pooled procurement)	- Offers the world lowest vaccine prices to Gavi-countries - Favourable prices for other countries for basic/traditional vaccines + devices	Gavi, GPEI, MRI, Individual country governments, NGOs
Procurement, Advocacy, Coordination, Guidelines, Training	WHO EMRO	**PVP** - Approved in 2011 and launched in 2008. - Exploring the idea of a pooled procurement mechanism for countries of the EMR. - First stage: encourage countries to procure through UNICEF SD. This phase is on progress. - 2nd stage: countries to join the PVP mechanism, managed by EMRO. MoU have been sent to countries.	All countries of the region, especially MICs	Limited country commitment. The RO is waiting for stronger commitment from countries to move forward.	- The following countries have been procuring through UNICEF SD: Morocco, Lebanon. Egypt, Syria and Iraq have been also utilizing services of UNICEF SD on ad hoc basis. - The following countries have signed MoUs to participate in PVP: Lebanon and Iraq - Initiatives and ideas to help countries move forward could be explored	UNICEF SD, UNICEF MENARO PAHO, CDC, WHO HQ Individual EMR country governments

Sufficient, to be continued | Could be expanded/strengthened | Requires modifications | Not applicable, not enough information

Influencing market dynamics

Form of assistance	Org.	Activity name & Description	Countries covered	Challenges & limitations	Successes & development	Collaboration
Financing, Other	BMGF	BMGF actively engages in a number of initiatives working with several MIC manufacturers to support product development, product affordability, supply security and product PQ	MICs with domestic supply (eg. India, China, Indonesia, Brazil) and MICs where products are licensed or recommended		All countries benefit from entry of new products and manufacturers	Gavi
Technical and management assistance	CHAI	- Support developing country manufacturers enter or expand their presence in Gavi markets - Price negotiations with manufacturers - Support company's capacity for navigating PQ process	Gavi-countries	- Limited to Gavi countries - Challenges: developing country manufacturers not close to PCV production (> 5 years away) ; processes are long and impact of TA on timeline is limited	- CHAI could play a role in non-Gavi MICs - CHAI could provide more TA to manufacturers for WHO PQ process. - With the support of partners, CHAI has generated over US$1 billion in savings via negotiating lower vaccine prices for developing countries.	Gavi, several partners
Technical and management assistance, Financing, Advocacy	Gavi	**Supply & procurement strategy** - Engagement with manufacturers to advocate for expansion of capacity and new product development - Use of market shaping instruments: e.g. volume guarantees; prepayments	Gavi-countries	Creation of competitive markets is highly dependent on R&D success and long-term manufacturer commitment to vaccine development. It will not provide immediate relief	Market shaping role of Gavi may benefit MICs (creating healthy vaccine markets with competition which drives down prices)	UNICEF SD, BMGF, WHO
Advocacy, Procurement, Financing	Gavi	**ATAP: Access to Appropriate Prices** - Explore ideas and implement actions to provide access to appropriate prices in countries graduated from Gavi support (e.g., tendering mechanism; payment mechanism) - Seek commitments from manufacturers to continue providing access to the Gavi price to graduated countries for a set period of time - Explore the possibility to extend actions to non-Gavi LMICs	Gavi-graduated countries	- Focused on Gavi-graduated countries - Focused on near and mid-term (although can lay a foundation for long-term) - Incomplete participation of manufacturers on price commitments (in terms of time and vaccines covered), and potential requirement to procure through PAHO or UNICEF	- Currently being drafted and discussed - Could include non-Gavi LMICs	UNICEF SD and other partners
Meetings, Analysis	Harvard Global Health Institute	**Pricing policies & strategies** Research, analysis, and convening around options, policies and approaches to pricing in MICs - Convened two workshops of stakeholders in March and July 2014 to discuss this topic - Following the July workshop, it was decided to create a Working Group (WG) to focus the discussion on more technical aspects of the pricing debate, and this work is ongoing - Pending satisfactory progress by this WG, third workshop of stakeholders may be convened in the first half of 2015	All MICs	- No publicly available information on this work - Need to increase awareness of product options, prices paid in other countries, and conditions linked to various prices. - Need further research and analysis to understand components of vaccine prices		Several partners
Funding	USAID	**Research** Support to vaccine research development projects on malaria and HIV (IAVI)	All countries		USAID has supported malaria vaccine research for 20 years, contributing to successfully moving vaccines from the lab into field trials	IAVI, several partners
Advocacy, TA, Training,	WHO	**Local production** - HQ: supporting technology transfer for 13 countries for influenza	HQ: 13 countries EMRO: Egypt, Iran,		*No information on need or possibility to strengthen/expand activity*	

Monitoring		vaccine - EMRO: supporting Iran and Egypt for improving production capacity; supporting technology transfer for Egypt and Iran for influenza vaccine & IPV	Pakistan, Tunisia, Morocco			
Guidelines, Coordination	WHO (HQ)	**Product development** - WHO Preferred Product Characteristics (PPC) - Includes activities such as: collaboration, standards & guidelines, promotion of vaccine R&D (eg. MenA, VIMT on Malaria) - No direct involvement in tech transfer, except through initiatives with other partners, like PATH (eg. MenA) or for influenza - Works to strengthen NRAs, including in producing countries	LICs &MICs	Need to strengthen NRAs		
TA, Research	WHO (HQ)	**Research Agenda** - Strengthen country capacity to carry out implementation research - Monitor and map implementation research activities - Provide a platform for researchers to share results	All countries			
Policy analyses, TA, Financing	World Bank Group	- Analyses of financing and procurement of commodities and vaccines during provider payment and more broadly health financing reforms, in particular, the transition from supply to demand financing (e.g. introduction of health insurance) within often highly fragmented health systems - International Finance Corporation (IFC)	- Case study countries to be selected - IFC: China, India, Brazil	- Not limited to vaccines - IFC pharma portfolio does not yet include vaccines, but does include APIs and finished generic formulations, as well as an investment fund	Assessment available in Q3/2015	Gavi

Annex IV: Detailed list of proposed activities of MIC Strategy

	Strengthened decision making for timely and evidence-based immunization policy & programmatic choices		**Increased political commitment & financial sustainability** of immunization programmes		**Enhanced demand for & equitable delivery of immunization services**		**Improved access to affordable and timely supply**	
Continue existing efforts							*Increasing access to RF & strengthening pooled procurement options* • Continuing activities of the PAHO revolving fund for the American region • Continuing to conduct single country tenders at the request of countries *Increasing price Information* • Continuing sharing of price information through pooled procurement mechanisms • Continuing data collection and dissemination through the V3P • Continuing advocacy work for greater price transparency	PAHO RF WHO, PAHO RF, UNICEF, MSF
Increase scope of existing efforts	• Establishing & strengthening NITAGs, including through the development of an international network of NITAGs • Strengthening national capacity to generate evidence for decision-making including through provision of limited operational funding to countries	WHO, SABIN, AMP	• Strengthening legislative basis for immunization • Advocating for immunization to achieve set immunization spending targets (to be developed) • Targeted advocacy and technical assistance for resource mobilization and increased efficiency in resource use	WHO, SABIN	*Strengthening in country supply chain & data systems* • Promoting the use of the comprehensive EVM strategy and building capacity • Optimizing supply chain systems through the use of private sector engagement and innovative partnerships • Creating a peer learning platform on national immunization data • Providing targeted support that focuses on the introduction of e-registries and other data challenges identified (harmonization, urban immunization, private sector engagement…)	WHO, UNICEF, AMP	*Increasing access to RF* • Expanding the capital base of Vaccine Independent Initiative (VII) through 2020 • Increasing country subscription to VII through proactive outreach • Increasing access of countries to commercial markets bank guarantees *Harmonizing product choice & registration processes* • Developing and establishing WHO norms and standards • Facilitating alignment of registration requirements and simplification of registration procedures, including through the use of 'facilitated/expedited process' for prequalified vaccines • Facilitating registration of PQ vaccines through collaborative agreements with NRAs	UNICEF, WHO WHO

New proposed efforts			*Addressing vaccine hesitancy & building community demand through:* • Creating a network of centres of excellence to build the necessary expertise for country support • Developing and strengthening tools addressing vaccine hesitancy • Evaluating and tailoring the TIP framework to middle income settings	WHO, AMP	*Increasing procurement skills and knowledge* • Supporting south-to-south vaccine procurement learning through an annual Exchange Forum , regional workshop, and a vaccine Procurement Network • Providing in-country technical assistance on procurement, including through the establishment of a pool of vaccine procurement experts • Developing vaccine procurement guidelines & advocating for public procurement reform • Strengthening demand-supply information exchange through current initiatives *Strengthening pooled procurement options* • Synthesizing lessons learnt from ongoing efforts (UNICEF MICs tender, PAHO RF, EMRO PVP) • Piloting a new tendering approach focusing on country demand consolidation possibly at regional level *Influencing Market Dynamics* • Encouraging the use of access agreements to the benefit of non-Gavi MICs including through the Gavi ATAP initiative • Influence market dynamics through UNICEF and PAHO RF tendering processes	UNICEF, WHO, and WB (TBD)

Annex V: Acronyms

AMP ..... Agence de Médecine Préventive
AMRO ..... WHO Regional Office for the Americas
ATAP ..... Access to appropriate prices
BCG vaccine ..... Bacillus Calmette-Guerin vaccine (tuberculosis)
BID ..... Better Immunization Data
BMGF ..... Bill & Melinda Gates Foundation
CHAI ..... Clinton Health Access Initiative
CHERG ..... Child Health Epidemiology Reference Group
CSO ..... Civil society organization
DCVMN ..... Developing Countries Vaccine Manufacturers Network
DTP3 vaccine ..... Diphtheria-Tetanus-Pertussis vaccine
EMRO ..... WHO Regional Office for the Eastern Mediterranean
EURO ..... WHO Regional Office for Europe
EVM ..... Effective Vaccine Management
GGE ..... General government expenditure
GVAP ..... Global Vaccine Action Plan
HPV ..... Human papillomavirus vaccine
HVAC ..... Heating, ventilation, air-conditioning
IARC ..... International Agency for Research on Cancer
IDS ..... International Debt Statistics
IFPMA ..... International Federation of Pharmaceutical Manufacturers & Associations
IPV ..... Inactivated poliovirus vaccine
IVAC ..... Johns Hopkins University International Vaccine Access Center
JRF ..... WHO/UNICEF Joint Reporting Form
LICs ..... Low income countries
LMICs ..... Lower middle income countries
OPV ..... Oral poliovirus vaccine
MCV1 ..... Measles-containing vaccine
MICs ..... Middle income countries
MR vaccine ..... Measles-Rubella vaccine
MSF ..... Médecins Sans Frontières
NICE International ..... National Institute for Health and Care Excellence International
NITAG ..... National Immunization Technical Advisory Group
NRA ..... National Regulatory Authority

NUVI .....New and Under-utilized Vaccines Implementation

PCV .....Pneumococcal conjugate vaccine

PAHO ..... Pan American Health Organization

PQ..... WHO pre-qualified product

RF ..... Revolving fund

SAGE ..... Strategic Advisory Group of Experts on Immunization

SEARO.....WHO Regional Office for South-East Asia

TA .....Technical assistance

TFGH..... Task Force for Global Health

TIP .....Tailoring Immunization Programme

UNICEF PD ..... United Nations International Children's Fund, Programme Division

UNICEF SD ..... United Nations International Children's Fund, Supply Division

USAID ..... United States Agency for International Development

V3P Project..... Vaccine Product, Price and Procurement Project

VII ..... Vaccine Independence Initiative

VPD.....Vaccine-preventable death

WHA ..... World Health Assembly

WHO.....World Health Organization

WPRO ..... WHO Regional Office for the Western Pacific

WUENIC..... WHO/UNICEF Estimates of National Immunization Coverage

Draft framework for formulating recommendations for the deployment of Ebola vaccines

SAGE Working Group on Ebola Vaccines and Vaccination, March 2015

Contents

Abbreviations:

ECBS Expert Committee on Biological Standardization

EUAL Emergency Use Assessment and Listing

EVD Ebola Virus Disease

FLW Front Line worker

HCW Health Care Worker

SAGE Strategic Advisory Group of Experts on Immunization

WG Working Group

WHO World Health Organization

Background

In response to the ongoing widespread outbreak of Ebola Virus Disease (EVD) in West Africa, the World Health Organization (WHO) coordinated an effort to accelerate the development of vaccines against EVD for use in the current outbreak, as well as in response to future outbreaks.

In October 2014, the WHO Director General requested the Strategic Advisory Group of Experts (SAGE)[1] on Immunization to advise WHO on the large-scale use of the vaccine(s) in the context of one or more vaccines receiving regulatory or emergency authorization for use. In response to this request, the WHO SAGE secretariat established a Working Group with an urgent program of work to facilitate a SAGE review of the available and emerging evidence to inform the development of the recommendations for the use of Ebola vaccines (see Annex 1 for TOR of the SAGE WG).

The urgency of the task required that the SAGE Working Group process to review the available evidence and draft recommendations should proceed in parallel with the ongoing phase 1, phase 2 and phase 3 trials of candidate vaccines, before any substantive safety and efficacy data for the vaccines were available. Furthermore, the product characteristics of the vaccines most likely to be available for early deployment would pose a significant challenge to large scale deployment in countries with limited infrastructure, creating an additional dimension to consider when drafting recommendations for widespread use.

The lack of complete clarity on the requirements and timelines for the authorization for use of Ebola vaccines, including emergency authorization, represents an additional challenge for the Working Group. A consultation on draft guidelines on the scientific and regulatory considerations for the evaluation of vaccines for use in public health emergencies is ongoing prior to presentation to the WHO Expert Committee on Biological Standardization (ECBS).[2] Additionally, a public consultation on a process for Emergency Use Assessment and Listing (EUAL) of vaccines to be used during Public Health Emergencies of International Concern (PHEIC) is also underway.[3] The unprecedented urgency given to all these activities reflects the devastating impact of EVD, and the need to have recommendations for use, should a vaccine that satisfies the regulatory requirements for expanded use outside of clinical trials, whether approved or authorized for an emergency use only, become available and be needed based on the status of the outbreak.

The SAGE WG has held three teleconferences aimed at updating the members on the epidemiology of the current outbreak and the status of vaccine development. In order to draft a framework for formulating recommendations, the WG held its first face-to-face meeting on March 9-10, 2015, when it reviewed the latest available epidemiological data on the current outbreak, the status of vaccine development, including preliminary results from the phase 1 trials[4] [5] and the status and

[1] Strategic Advisory Group of Experts (SAGE) on Immunization- http://www.who.int/immunization/policy/sage/en/
[2] WHO Expert Committee on Biological Standardization. http://www.who.int/biologicals/expert_committee/en/
[3] Public consultation on emergency use assessment and listing procedures for medical products during public health emergencies: http://www.who.int/medicines/news/public_consult_med_prods/en/
[4] Ledgerwood, J. E., et al. "Chimpanzee Adenovirus Vector Ebola Vaccine - Preliminary Report." N.Engl.J.Med. (2014)

plans for the phase 2 and 3 trials. The WG was also briefed on the preparations for supporting countries with the deployment of vaccines and for monitoring their safety and effectiveness post-introduction, the responses from local communities with regards to vaccine research, and on predictive mathematical models on the future course of the outbreak and the potential impact of different vaccination strategies for the different vaccine candidates. One of the key expected outcomes of the meeting was the development of a draft framework for drafting policy recommendation for vaccine use that SAGE could consider.

This first draft of this framework is summarized below and provides an indication of the direction being taken by the Working Group. **The group consensus was that currently available data on any vaccines are too limited to allow any recommendations for use at this time**. Thus, the **framework should not be regarded as WG recommendations for immunization** with any Ebola vaccine now or future **but as a potential roadmap for further deliberations** and actual recommendations once data, and results of regulatory review, are available.

While developing the framework, the Working Group agreed that there were **a few overarching issues** that **needed to underpin the vaccine specific recommendations**. These include:

1. The need to stress the importance of the continued focus on other control measures that are known to be effective, even while deploying vaccines.
2. The need to continue efforts to re-establish routine childhood immunization in parallel to Ebola vaccine deployment, i.e. one should not be at the expense of the other.
3. Use the opportunity of Ebola vaccine deployment to strengthen health systems, e.g. disease and safety surveillance

Draft framework for formulating policy recommendations

When developing the draft framework, the Working Group considered the following issues in sequence:

1. Defining a variety of epidemiological scenarios for framing the recommendations.
2. Establishing the objectives for immunization in each scenario.
3. Defining and prioritizing the target populations for vaccination under each scenario.
4. Defining additional considerations that need to be addressed when making recommendations.

Epidemiological scenarios

The Working Group recognized that the risks and benefits of vaccination, particularly with a vaccine that has not had full regulatory licensure, will vary depending upon the status of the epidemic at the

[5] Rampling, T., et al. "A Monovalent Chimpanzee Adenovirus Ebola Vaccine - Preliminary Report." N.Engl.J.Med. (2015).

time vaccination is being considered for deployment. For example, potential benefits are likely to be higher, and uncertainties about safety and efficacy more acceptable, in considering recommended uses during a widespread outbreak that is not coming under control as compared with situations where cases are sporadic or declining. Recommendations were therefore organized according to different epidemiological scenarios to assess the different needs and respond most effectively under the circumstances. These were pitched to try to categorise different levels of public health emergency, as well as different patterns of spread. The initial categorization of the epidemiological scenarios for framing recommendations is summarized in Table 1.

In view of the fact that none of the vaccine candidates might reach full licensure, and, therefore, recommendations may have to be made for a vaccine authorized for emergency use only, the Working Group subdivided the recommendations for use under each epidemiological scenario into two subcategories: 1) if authorization was for emergency use only [6] [7] [8] and thus potentially only valid for a limited period of time or for a smaller set of indications, and subject to certain post-marketing conditions; and 2) if one or more fully licensed vaccines were available. In general, given that an emergency use process would, by definition, not provide conclusive information on efficacy and/or safety, and thus presents more uncertainty, the WG felt that use of a vaccine made available under such a provision is likely to be relatively more targeted and limited than use of a fully licensed vaccine.

Table 1. Epidemiologic scenarios for framing Ebola vaccine recommendations

Epidemiological scenarios		**Authorization for use**	
		Emergency	**Full licensure**
Widespread transmission of disease	Increasing disease trend		
	Flat trend		
	Declining trend		
Localized or limited transmission			
Countries/ communities with no reported cases but at high risk from an ongoing outbreak, e.g. neighbouring countries			
Future outbreaks	Reactive vaccination		
	Preventive vaccination		

[6] US FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf)

[7] European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP). Guideline on the scientific application and practical arrangements necessary to implement commission regulation (EC 507/2006) on the conditional marketing authorization for medicinal products for human use falling within the scope of regulation EC 726/2004. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004908.pdf

[8] Health Canada. Guidance document – submission and information requirements for extraordinary use of new drugs (EUNDs)

Four different epidemiological scenarios were considered. Three of the scenarios were in the context of the ongoing outbreak in West Africa. The fourth related to use of vaccine for responding to or preventing future outbreaks.

1. The first scenario included countries or communities with widespread transmission, e.g. the three most affected countries in the current outbreak in West Africa. Given the evolution of the epidemic in each country, it was felt that this scenario should be further divided into subcategories reflecting the status of the outbreak and the shifting risk-benefit balance of introducing vaccines with limited or varying levels of data on safety and efficacy.
2. The second scenario included countries (or communities) with one or more reported cases, but with limited or no further transmission (e.g. countries such as Senegal, Mali and Nigeria in the context of the current outbreak).
3. A third scenario included countries (or communities) with no reported cases, but at high risk of importation of cases (e.g. countries neighbouring the most affected countries in the context of the current outbreak and with significant cross-border population movement).
4. The fourth scenario included recommendations for the use of the vaccine in future outbreaks. This scenario was further divided into two subcategories. The first related to reactive vaccination in response to a future outbreak, including the creation of a vaccine stockpile with rapid release and deployment of vaccine in response to an outbreak. The second subcategory included preventive vaccination in individuals, communities or countries considered to be at high risk for acquiring EVD, for example countries with reported past outbreaks of EVD or with other risk factors that might lead to an outbreak.
5. Recommendations for use of the vaccine in each scenario would include vaccination of travellers to outbreak affected countries, especially all front line volunteer health care and laboratory workers and non-travellers who may be at increased risk, such as laboratory workers in unaffected countries, who may handle potentially infected materials.

Prioritization of the scenarios for drafting recommendations

Given the tight timelines, the Working Group considered prioritizing the formulation of recommendations under each scenario and whether these could be sequenced. Given the status of the clinical trials, it was felt that any recommendations for early deployment would be preliminary and are likely to be implemented in the context of emergency use authorization, which was likely to only allow limited use of the vaccine accompanied by post-marketing conditions, with such use focused on individuals or communities at highest risk. However, it was understood that the regulatory pathways were still under discussion, that the situation might change and that this draft approach may need to be revisited.

Under the circumstances, and with the low likelihood that efficacy data would be available in the short term, the Working Group agreed to focus its effort on formulating recommendations on use of the vaccine in the context of the ongoing outbreak. Formulation of recommendations on future use of the vaccines could be deferred until additional data were available on the safety, immunogenicity and efficacy (either directly observed or inferred based on a correlate of protection), the regulatory processes were more clearly defined, and there were more data on the programmatic suitability of the different candidates.

Objectives of vaccination

The Working Group considered the following objectives for use of vaccination:

1. Interruption of transmission, i.e. elimination of disease
2. Mortality reduction
3. Preservation of essential services (i.e. health, security, government)
4. Individual protection of the highest risk groups, e.g. front line health workers and lab personnel

The Working Group was of the opinion that any objective short of disease elimination (i.e. interruption of transmission) was unlikely to be acceptable in the context of the current epidemic given that all other EVD outbreaks have ended with disease elimination. In parallel to these primary objectives, individual protection would need to be considered as an objective in a scenario when vaccine supplies are limited and/or where the risk/benefit data on an EU vaccine may not be sufficient to support wider use in less at-risk populations and vaccine may be deployed mainly for the individual protection of the highest risk groups (e.g. front line workers). Individual protection may also be the main objective for laboratory personnel in non-endemic countries who may handle potentially infected specimens.

Based on these considerations, the Working Group proposed the following objectives for vaccination under all epidemiologic scenarios, within the context of the current outbreak:

Primary objective: Interruption of transmission leading to the complete control of an outbreak (i.e. elimination)

Secondary objective: Individual protection of high-risk individuals. This would be particularly relevant when vaccine supplies were limited or data to assess risks and benefits in population groups at lower risk were not available.

Target populations for vaccination

Based on the information reviewed during the meeting, the Working Group initiated the process of defining target populations to be prioritized for vaccination. **It was, however, recognized that this list must be considered provisional and illustrative at this time and will need to be revisited as new evidence that might influence this prioritisation becomes available on the vaccine candidates, the status of the epidemic, on the risk of disease in different population groups, and on the social contexts that affect the balance of risks and benefits**. A review of these recommendations will be undertaken by the WG before final presentation to SAGE.

Available evidence presented at the meeting suggested that health workers (medical doctors, nurses, midwives and laboratory workers) were 20-40 times more likely to get infected than non-health workers. While the attack rates in this group have declined, they remain at substantially higher risk of disease than those not in these fields of work. This group is essential to providing ongoing care of other affected individuals while they are exposing themselves to increased risk while providing this care. The principle of reciprocity thus provides ethical support to this approach. Hence, this group was considered as the highest priority for vaccination under all scenarios.

In the context of widespread transmission of virus a similar priority may be given to other front line workers involved in the Ebola response (burial teams, contact tracers, community workers etc.). Further data on the magnitude of risk in this category of workers is being sought to make informed recommendation.

Additional analysis of the data will be required to determine the different categories of workers to be included among "health care workers" and "other front line workers" and the relative risk of disease in each category of workers in order to assess the risks and benefits of vaccination and prioritize them accordingly.

Next in priority were adults 15 years and older (the exact age range to be defined based on additional analysis of the epidemiologic data), who have been shown to have a much higher incidence of disease than children and appear to be more likely to transmit disease as compared to children. Mathematical models indicate that vaccinating adults would have a higher impact on preventing disease in children and that the additional vaccination of children would have relatively little incremental benefit. **However, updated data from the models that are periodically updated would need to be considered in prioritizing target groups when actually framing recommendations**. Nevertheless, social and community considerations might require the vaccination of children for individual protection, should a safe and effective vaccine become available for this age group. Whether the use of vaccine in this adult priority group would be targeted (e.g. ring vaccination, in high risk districts) or universal would depend on the nature of the epidemic and the availability of vaccine, with targeted vaccination likely to enjoy higher priority than universal vaccination.

The tentative definition and prioritization of target groups for vaccination under each scenario are summarised in Table 2. However, it may be stressed once again that **these are meant to be illustrative and intended to provide SAGE with a sense of the direction being taken. This prioritization will need to be reviewed and refined, based on a more comprehensive review, compilation of the data, and GRADE-ing of the evidence (where appropriate)**. Prioritization was only considered, albeit very briefly, for target groups within the context of the current outbreak.

Table 2. Illustration of the definition and prioritization of target populations under each scenario (actual recommendations will be based on available evidence at time of consideration of use of an emergency use or licensed vaccine)

Epidemiological scenarios		Target population (ILLUSTRATIVE ONLY)	
		Emergency Authorization	**Full licensure**
Widespread transmission of disease	Increasing disease trend	FLW	FLW
		Adults (targeted)	Adults (targeted)
			Universal
	Flat trend	FLW	FLW
		Adults (targeted)	Adults (targeted)
	Declining trend	FLW	FLW
			Adults (targeted)
Localized or limited transmission		HCW	HCW
		Adults (targeted)	Adults (targeted)
Countries/ communities with no reported cases but at high risk from an ongoing outbreak		None	HCW

HCW= Health care workers (e.g. doctors, nurses, laboratory workers, cleaners in Ebola Treatment Units)

FLW=Front Line Workers= HCW + burial teams, contact tracers, community care givers, etc.[9]

The vaccination of the adult population was further subdivided into:

1. Targeted vaccination, i.e. vaccination targeted by geography (most affected communities) or by chain of transmission (e.g. ring vaccination – vaccination of contacts and potential contacts of contacts).
2. Universal vaccination of all eligible individuals throughout the country.

Additional considerations while formulating recommendations

There was consensus within the working group that additional issues needed to be taken into consideration, in particular stressing the importance of continued focus on the non-vaccination prevention and control strategies. In the absence of vaccine effectiveness data, it is particularly important to ensure that these measures continue to be prioritized and implemented as effectively as possible and that there is no relaxation of these efforts despite the potential for deployment of vaccines. Conversely, It was pointed out that based on the evolution of the epidemic in Liberia, it is possible to stop this epidemic without vaccine and that if an investigational vaccine had been used in Liberia, many would have erroneously concluded that it worked and stopped the epidemic.

These considerations, as was the case with the definition and prioritization of targets groups, were not discussed in detail at the meeting and would be the subject of future teleconferences and meetings of the Working Group.

[9] The categories of workers classified as FLW may evolve based on further analyses of epidemiological data

The following issues have been tentatively listed for the consideration of the Working Group:

1. Recommendations on disease and safety surveillance to accompany deployment of vaccines.
2. Recommendations on managing febrile episodes following vaccination (especially when vaccination targets potential contacts of cases as part of a ring vaccination strategy).
3. Recommendations on community engagement and risk communications to improve the uptake of vaccines by the target populations.
4. The potential trade-offs and how should they be addressed, for example:
    a. Between vaccines or schedules that rapidly induce protection versus those that provide longer duration of protection?
    b. Between efficacy and programmatic feasibility, e.g. choosing between the vaccine with highest efficacy versus one that is programmatically more easily deployed but has lower efficacy?
5. The non-vaccination control measures that needed to be stressed.
6. Considerations for vaccine deployment in the face of ongoing enrolment in phase 3 vaccine trials.
7. The need for continued focus for re-establishing routine childhood immunization in parallel deploying Ebola vaccines

Geographical aspects

The importance of prioritizing vaccination in specific settings affected by the disease was highlighted in the meeting. Widespread vaccination campaigns would be difficult to implement, could be limited by the total number of doses needed and cold chain requirements, and might not respond to the geographical distribution of EVD cases. Cluster (ring) or locally targeted vaccination might be an asset if EVD outbreaks are in small clusters or affect only certain regions and not widespread, thereby preventing more cases in specific communities and neighbouring populations. The thermostability and the presentation and packaging of the currently available candidates may limit the ability to deploy them widely in countries with limited infrastructure. Ring or targeted vaccination would help overcome some of the infrastructural barriers by limiting vaccination to specific settings where they are likely to have the biggest impact.

Next steps

1. Further develop and refine the framework based on feedback from SAGE, through on-going discussions of the WG during teleconferences, and a second face-to-face meeting if required. These discussions will be informed by additional analysis of the epidemiological data, the further

evolution of the current outbreak, and further clarity on the scope and timelines for the regulatory processes. It will also be essential that complete and detailed information is made available from the vaccine trials, in particular how the study designs and primary outcome measures of the phase 3 trials are being adapted to the changing epidemiology and how they will provide the evidence of safety and immunogenicity/efficacy critical to inform Public Health decision making..

2. Develop timelines for having a first draft set of recommendations for presentation to SAGE (which will most likely focus on use in the context of current epidemic) either at its next meeting in October 2015, or, if required, at an extraordinary meeting specifically to discuss the Ebola Vaccination recommendations.

Request to SAGE

SAGE is requested to consider the proposed framework for drafting recommendations for use for Ebola vaccines and provide its input for the further development and refinement of this framework.

ANNEX

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

Terms of reference of the Working Group

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:

- Reviewing the essential evidence required for making policy recommendations and on strategies for deployment of vaccines.
- Reviewing the available epidemiological data to define the risk of disease and mortality in different population groups in order to allow prioritization of vaccination.
- 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.
- Reviewing the data on the projected impact of different vaccination strategies generated by mathematical models.
- Reviewing the synthesis of the above data for presentation to SAGE and in drafting recommendations for consideration by SAGE.
- Reviewing the projections of vaccine supply to inform recommendations on the deployment of vaccines.

Composition

- Rees, Helen (Co-Chair, Chair of the African Task Force on Immunization (TFI)); Executive Director - Reproductive Health Research Unit, University of Witwatersrand, South Africa; Chair South Africa Medicines Control Council.
- Tomori, Oyewale (Co-Chair, Member of SAGE); Professor of Virology, Redeemer's University, Nigeria.
- Andrews, Nick; Deputy Head of Statistics Unit, Public Health England, UK.
- Bonsu, George; Immunization program manager Ghana, Ghana.
- Durrheim, David; Hunter New England Area Health Service and Professor of Public Health, Australia
- Goodman, Jesse; Professor of Medicine, Georgetown University, USA

- Jemmy, Jean-Paul; Medical Coordinator of Operations, Médecins San Frontières, Belgium
- Kelly, Ann; Senior Lecturer in Anthropology, Department of Philosophy, Sociology, and Anthropology, University of Exeter, UK.
- Moodley, Keymanthri; Director, Centre for Medical Ethics and Law, Department of Medicine, Stellenbosch University, South Africa.
- Ndack, Diop: Lecturer in Socio-Anthropology & Methodology of research in social science. University Cheikh Anta Diop, Dakar, Senegal
- O'Brien, Kate (Member of SAGE); Professor, Department of International Health & Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, USA.
- Ockenhouse, Chris; Director, Medical and Clinical Operations, Malaria Vaccine initiative, PATH, USA.
- Velasco Muñoz, Cesar; Preventive Medicine and Epidemiology Unit, Hospital Clínic-Universitat de Barcelona-Barcelona Centre for International Health Research, Barcelona, Catalonia, Spain. /Surveillance and Response Support, European Center for Disease Control, Sweden.
- Were, Fred (Member of SAGE and member of TFI); Executive Director - Professor, Department of Paediatrics and Child Health, University of Nairobi, Kenya
- Wiysonge, Charles (Member of TFI); Professor in Community Health Stellenbosch University; Deputy Director Centre for Evidence-based Heath Care Stellenbosch University, South Africa

Ex-Officio members

- Breiman, Robert; (Chair of WHO Immunization and vaccines related implementation research advisory committee (IVIR-AC))
- Griffiths, Elwyn; (Chair of WHO Expert Committee on Biological Standardization (ECBS))
- Morgan, Chris; (Chair of WHO Immunization Practices Advisory Committee (IPAC))
- Wharton, Melinda; (Chair of WHO Global Advisory Committee on Vaccine Safety (GACVS))

WHO Secretariat

- Focal point: Cherian, Thomas

Link to the website: http://www.who.int/immunization/policy/sage/sage_wg_ebola_nov14/en/

Interim Report to WHO Initiative for Vaccine Research

WHO TASKFORCE TO EVALUATE INFLUENZA DATA TO INFORM VACCINE IMPACT AND ECONOMIC MODELLING

24 March 2015

Executive Summary

As part of the WHO maternal influenza immunization agenda, the WHO Initiative for Vaccine Research (IVR) convened a Taskforce during 2014 to advise in the review of key variables for influenza vaccine impact and health economic modelling studies. The Taskforce is a working group of the WHO Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC) and functions as one of the sub-groups of the WHO Vaccine Preventable Disease (VPD) Burden and Impact Assessment Framework.

The Taskforce has three Workstreams; each is led by a different team reviewing influenza disease risk and morbidity in pregnant women, children <6 months of age, and the fetus, as well as vaccine performance to reduce influenza disease in these groups. Supporting data have been sought from a review on vaccine performance being conducted by the Aga Khan University and from clinical trials of influenza vaccine during pregnancy conducted in South Africa, Nepal, and Mali; however, data from the latter two of the clinical trials are not included in this report. Within the three Workstreams, the Taskforce has four objectives: 1) to determine key parameters needed for influenza vaccine impact and health economic modelling studies, with a focus on pregnant women and low-resource settings; 2) to determine evidence-based assumptions for these key parameters; 3) to evaluate the quality of existing data; and 4) to provide recommendations to WHO for addressing data gaps. The Taskforce will focus primarily on burden measures such as incidence (or attack rate) for influenza virus infection, symptomatic disease, hospitalization, and mortality; within the Fetal Effects Workstream, burden measures include risk (cumulative incidence rates) of preterm or small-for-gestational age birth and fetal loss, along with relative differences in these measures comparing women with and without influenza illness. For each Workstream, the lead investigator is conducting a systematic literature review and findings have been presented to a large group of experts – the members of the broader Taskforce – to obtain feedback on methodology, analysis, and interpretation. This report is written by the Taskforce Chair, Bradford Gessner (AMP), the Workstream Leads are Niranjan Bhat (PATH), Deshayne Fell (McGill University), and Mark Loeb (McMaster University), and the Taskforce Rapporteur, Mark Katz (Independent Consultant).

For the review of burden among pregnant women, no results are available currently. A secondary analysis evaluated risk of severe influenza among pregnant women. Based on meta-analysis of 148 comparative observational studies of people with influenza virus infection comparing pregnant women to either all other persons or less frequently all other women of child-bearing age, pregnancy was associated with hospitalization (odds ratio [OR], 2.9; 95% CI, 1.6 to 5.5) but not mortality (OR, 1.0; 95% CI 0.81 to 1.3), pneumonia (OR, 1.8; 95% CI, 0.72 to 4.5), receipt of

mechanical ventilatory support (OR, 1.2; 95% CI, 0.70 to 2.1), or ICU admission (OR, 0.89; 95% CI, 0.65 to 1.2). All outcomes except hospitalization were considered to have a low quality of evidence.

Among children <6 months of age, 22 studies provided data, including 14 studies from a previously published review. A meta-analysis of the 14 original studies found a pooled incidence of severe or hospitalized influenza of 3.1 per 1000 child-years (95% CI, 2.3 to 4.2). While most studies had incidences between 1 and 10 per 1000 child-years, the range extended from 0.62 to 17 per 1000 child-years when including more recent studies. A second review of influenza disease burden in this age group is ongoing. Preliminary findings include limitations in the number of high quality studies.

For evaluation of fetal effects comparing pregnant women with and without influenza illness, 20 comparative observational studies were included that compared one or more relevant Taskforce outcome among pregnant women with influenza virus infection (defined clinically or microbiologically) to pregnant women without influenza virus infection. Ten studies originated from the United States and the remainder from Canada or Europe, and studies used various methods to assign influenza status. Among six high-quality studies reporting data on preterm birth (gestational age <37 weeks), baseline preterm birth rates among uninfected women varied from 5.4% to 12% while rates among influenza-infected women varied from 7.2% to 24%. Three of these studies reported data for severe illness due to pandemic 2009 H1N1 with adjusted odds ratios of 1.3 to 4.0, with two studies reaching statistical significance. Influenza did not increase risk of preterm birth in two studies of pandemic 2009 H1N1 that evaluated a range of maternal illness severity, nor in two studies from non-pandemic seasons (one study each on severe and mixed severity seasonal influenza). Among four studies reporting low birth weight (<2,500 grams) that adjusted for gestational age, there were no significant differences between exposure groups (range in odds ratios, 1.1 to 1.3). Two high-quality studies provided data on fetal loss, both involving pandemic 2009 H1N1 with one finding a risk ratio of 4.2 (95% CI, 1.4 to 12) and one 1.9 (95% CI, 1.1 to 3.4).

For the evaluation of vaccine efficacy in pregnant women and their children <6 months of age, the Taskforce is taking advantage of two systematic reviews of influenza vaccine performance in pregnancy. The Taskforce will meta-analyse the highest quality evidence from these reviews to estimate vaccine efficacy as outlined in the activity objectives. Review of the literature has identified only one randomized clinical trial with pre-specified laboratory-confirmed influenza disease endpoints. In the identified randomized clinical trial, 2116 pregnant women without HIV and 194 pregnant women with HIV were enrolled in Soweto, South Africa. The primary clinical endpoint was mild, acute respiratory illness with laboratory confirmation of influenza virus infection. Vaccine efficacy was identified for this outcome for HIV-infected and uninfected women and HIV-uninfected children age <6 months. There were no reported differences in terms of vaccine impact on severe influenza disease in mothers or children <6 months of age. Among newborns (both exposed and unexposed to HIV), there was no statistical difference between vaccine groups for low birth weight, median birth weight, miscarriage (fetal death <28 weeks), or stillbirth (fetal death ≥28 weeks).

Evaluations are continuing, and results will be updated in the future for all Taskforce activities. Based on the existing data, several conclusions can be reached.

- **Interpretation and comparison:** Few data exist on the burden of influenza-associated outcomes following infection during pregnancy to the pregnant woman, fetus, or newborn. Many studies that have been conducted have methodological issues that make

interpretation difficult. Comparison across studies is difficult due to differences in case definitions (including methods for ascertaining influenza), period of assessment during pregnancy, and potentially different effects of pandemic 2009 H1N1 compared to other influenza strains or years.

- **Influenza risk and burden in pregnant women:** In predominantly high-income settings, influenza increases the risk of hospitalization, but not of severe disease, among pregnant women.
- **Influenza risk and burden in children <6 months of age:** There are limited published data on influenza disease risk and burden in children <6 months of age. Many of these studies are small or have methodological issues, which limit their utility in estimating the burden of severe influenza disease in this group.
- **Influenza risk to developing fetus:** There are limited published data from comparative studies on the risk of maternal influenza disease on birth outcomes, and they have methodological differences and limitations, which make interpretation a challenge. There is some replicated evidence from higher-quality studies suggesting that severe pandemic 2009 H1N1 disease – but not mixed severity disease or disease due to seasonal influenza – during pregnancy was associated with preterm birth. Studies of mild or subclinical maternal influenza disease did not show an association with preterm birth during the 2009 pandemic or during non-pandemic seasons.
- **Vaccine efficacy to prevent influenza disease:** There are limited high quality published data from randomized clinical trials; however additional clinical trial data are expected soon. Evidence from one large adequate quality trial on the effectiveness of inactivated influenza vaccine during pregnancy suggests reduced laboratory-confirmed influenza among women and their babies, but no evidence was found of impact on severe influenza disease or on newborn outcomes. More well-designed, large scale randomised controlled trials are needed with appropriate controls to establish the benefit of maternal influenza vaccination during pregnancy.

Taken as a whole, influenza disease burden data may not be sufficient to inform decision-making in many countries regarding routine immunization of pregnant women with influenza vaccine. This situation is particularly true for low-resource settings, where results may differ substantially due to differences in influenza epidemiology, background prevalence of underlying diseases, severity of disease on presentation, likelihood of secondary bacterial infection, and background prevalence of adverse fetal outcomes. Without baseline disease burden estimates, including vaccine preventable disease incidence against severe clinical outcomes such as pneumonia or respiratory disease deaths, the public health utility of incorporating influenza vaccine into national immunization programs remains unknown.

The full Interim Report of the **WHO Taskforce to Evaluate Influenza Data to Inform Vaccine Impact and Economic Modelling** can be found at the IVR website: http://www.who.int/immunization/research/meetings_workshops/taskforceinterimreportMarch2015/en/

Report from the SAGE Working Group on Pertussis vaccines
26 - 27 August 2014 meeting
Geneva, Switzerland

Participants of the meeting:

Pertussis Working Group Members:

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Background

In March 2013, in the light of a recent increase in reported pertussis cases from some countries, which was in some instances associated with an increase in infant deaths, SAGE and WHO agreed that a new working group on pertussis vaccines would be established to prepare for a SAGE review of the evidence that would lead to updating as needed the 2010 WHO position paper on the use of pertussis vaccine[1] .This also provided an opportunity to review newly available data on effectiveness of various vaccination strategies aimed at reducing infant mortality, as well as the pertussis-related outcomes of the vaccine schedule optimization project.

The terms of reference for the SAGE pertussis vaccines working group were to:

1. Review epidemiological data on pertussis from selected countries using acellular pertussis (aP) and/or whole cell pertussis (wP) vaccines and evaluate the evidence for resurgence of pertussis, with an emphasis on severe pertussis in very young infants. In countries where the evidence supports resurgence, evaluate the evidence for the hypothesis that resurgence is due to shorter lived protection from aP relative to wP vaccines;

2. Review the evidence on effectiveness of 1 or 2 doses of pertussis vaccines against severe disease and death in young infants;

3. Review the evidence on effectiveness of three key strategies aimed at reducing severe disease and death from pertussis in very young infants (cocooning, maternal immunization during pregnancy, and immunization of newborns);

4. Review the evidence for optimal primary vaccination scheduling and timing of booster dose(s);

5. Review the evidence that changes in circulating pertussis strains have had an adverse impact on the effectiveness of aP or wP vaccines;

6. Propose updated recommendations for SAGE consideration on the use of pertussis vaccines.

The working group completed its review in relation to points 1, 2, 3, and 5, of its terms of reference in February 2014 and presented to SAGE on those points at the April 2014 SAGE meeting.

The review of the optimal primary immunization schedules as per point 4 of the terms of reference was, at that time ongoing, so the initial plan was that this would be presented at the October 2014 SAGE meeting. This review entailed a 4-component framework (epidemiology of the diseases, systematic review of the effectiveness and safety of the various schedules, operational considerations, and modelling) following the model already applied to pneumococcal conjugate, rotavirus and *Haemophilus influenzae* type b (Hib) vaccines. The initial intent was that both combined diphtheria, tetanus toxoid and pertussis vaccine (DTP) and tetanus toxoid vaccine (TT) schedules be reviewed by the pertussis working group, in view of the challenges of disentangling the primary vaccination schedule for pertussis from that of diphtheria and tetanus and the interrelation of the TT and DTP schedules. Point 6 of the terms of reference was to be fully completed only after completion of point 4.

[1] Pertussis vaccines: WHO position paper. WER 2010, 85, 385–400. http://www.who.int/wer/2010/wer8540.pdf).

As a result of SAGE's review of the evidence in April 2014, a brief revised guidance note on choice of pertussis vaccines was published in July 2014[2], with a plan to update the full position paper on the use of pertussis vaccines after the review of the evidence for optimal primary vaccination scheduling and timing of booster dose(s) would have been presented to SAGE.

Purpose of the August 2014 meeting and content of this report

The aim of the August 2014 meeting of the pertussis working group was to present the various components of the systematic reviews completed under the aegis of the schedule optimization project and to explore the implications of different vaccination schedules for diphtheria, tetanus and pertussis, recognizing that one single schedule would be unlikely to fit all settings.

Discussions focused mostly on the revision of the current ideal schedule for DTP with some discussions of TT and DT boosters.

The rationale for the pertussis working group being appointed for this task was first, that pertussis is an important driver of the schedules second, as stated above, it is hard to disentangle the primary vaccination schedule for pertussis from that of diphtheria and tetanus and third the interrelation of the TT and DTP schedules.

The key questions to be addressed were the number and timing of primary pertussis doses and their interval. Although during the meeting the pertussis working group and additional invited experts looked at the broader life course with much discussion on diphtheria and tetanus, the current report focuses on children and pertussis. It only presents diphtheria and tetanus related information that is essential to understand the drivers of the pertussis vaccine containing schedules in the context of the main aim of pertussis control at global level i.e. to reduce the risk of severe pertussis in infants and children.

Discussions on the overall duration of protection induced by adolescent and adult boosters, and how to ensure durable protection for tetanus and diphtheria are very complex. During the meeting, none of the data presented were informative in relation to booster schedules necessary to ensure continuous protection as compared to current recommendations/practices. Work will continue, to retrieve and interpret additional data, acknowledging the major limitations of the currently available data.

This report is to be read in conjunction with the "wP pertussis vaccines: research evidence on effects of various immunization schedules" produced by the London School of hygiene and Tropical Medicine (LSHTM) and inserted in the Yellow Book. This latter document contains more specific information related to the wP vaccine, which remains the priority for developing countries. The LSHTM report reflects any updated information related to wP that has become available since the August 2014 meeting of the pertussis working group. This report only briefly alludes to evidence with respect to wP vaccines, and refers to the LSHTM report for more detailed information.

[2] Revised guidance on the choice of pertussis vaccines: July 2014 WER 2014, 89, 337-344.

SAGE members are also invited to refer to the full systematic reviews shared at the August 2014 meeting and available on the SAGE password protected website. They are further advised to refer back to the report prepared for SAGE by the pertussis working group on 14 March 2014 and also available on the SAGE website[3].

Methods and information presented to the working group

Andrew Clark provided an overview of the current DTP schedules and the vaccines in use by country and WHO region.

Colin Sanderson reported on the actual age of vaccination and age-specific, coverage-related issues, as well as on the number of maternal Tetanus Toxoid (TT) vaccine doses received. A total of 66 Demographic Health Surveys (DHS) as well as 36 Multiple Indicator Cluster Surveys (MICS), mostly from lower and middle income countries within all WHO regions, were assessed, using only the most recent surveys from each country and only if the date of vaccination was reported for at least 40% of doses given. The data were mainly collected via interviews with mothers as well as assessments of their children's vaccination cards (data from cards preferred). In total 102 surveys were reviewed and 56 included. The 56 included surveys contained data on about 236,000 children aged 24 months and older. Age-specific coverage as an indicator of vaccine delay was assessed for time-points of receipt of BCG, DTP1-3 and measles containing vaccines (MCV).

Colin Sanderson also reported on the pre-vaccine and post-vaccine era distribution of pertussis cases by age. Relevant studies were identified through PubMed/Medline, the Cochrane Library, Embase, Web of Science and Scopus databases. In total 15 studies that contained age-specific data were identified. These covered 9 countries, 3 of them low income countries, during the post-war pre-vaccine). In some cases it was possible to present country specific data from both the pre and post vaccine era. Data were presented as a distribution of percentage of cases or deaths per week, versus age from the following countries: Sweden (pre- and post), Denmark (pre- and post), UK (pre- and post), Romania, Kenya (pre- and post), Senegal, South Africa, USA (pre- and post) and India.

Tejpratap Tiwari presented a review of historical data from the pre and post vaccine introduction era of industrialized countries. The objective of this review was to evaluate the age trend of diphtheria during the pre- and post- vaccine era and examine the evidence of age-group shifts in disease notifications. English-language databases (Web of Science Core Collection, Virtual Health Library, The Cochrane Library and WHOLIS) were searched without restriction in years. Historical national data were available from developed countries for the pre-vaccine era but data including age distribution was limited to studies from England and Wales, Germany, Scandinavian countries, the United States of America and Canada.

[3] WHO SAGE pertussis working group. Background paper. SAGE April 2014. Available at http://www.who.int/immunization/sage/meetings/2014/april/1_Pertussis_background_FINAL4_web.pdf?ua=1; accessed June 2014.

Martha Roper presented a summary of key points on the epidemiology of tetanus, with focus on age- and sex- specific differences in neonatal tetanus (NT) and non-neonatal tetanus (nNT) between the pre- and post-vaccine eras.

Judith Müller presented a systematic review of data on the comparative efficacy/effectiveness, immunogenicity and reactogenicity of DTP infant schedules (available on the SAGE web site). The objectives were to provide the best evidence on primary series vaccination with DTP vaccines among children <18 months and to compare the effect on outcomes of the number of doses, the age at initiation of vaccination, the length of vaccine dosing intervals and any schedule compared to no vaccination. Further objectives were to provide best evidence on booster vaccination with DTP vaccines among children <5 years and to compare the effect on outcomes of age at booster as well as any booster compared to no booster.

The systematic review was conducted according to Cochrane processes. Literature in English, French and German were taken into consideration. Relevant outcomes were clinical efficacy or effectiveness, immunogenicity and reactogenicity. Randomized controlled trials (RCTs) as well as observational studies (cohort or case control; surveillance) comparing $\geqslant$2 different schedules, vs. no vaccination, vaccine without DTP, or placebo, using the same immunization schedule or incidences before and after introduction or change in DTP schedule were taken into consideration. Comparisons between groups were only analyzed when they had the same surveillance protocol (or reasonably comparable groups) or the same vaccine product. Additional evidence from studies which were not-per-protocol contributed relevant evidence with regard to the study objectives but did not fulfil inclusion criteria for case definitions or serological methods. GRADE was used to assess the quality of the evidence. For diphtheria and tetanus vaccines, a total of 15 references were included (6 RCTs and 9 observational). An additional 9 not-per-protocol studies (3 RCTs and 6 observational) informed the review. These studies did not meet any exclusion criteria, contributed relevant evidence with regard to the study objectives, but did not fulfill all inclusion criteria, mainly those relating to outcomes i.e. case definitions and serological methods. .

Immunological correlates of protection were considered. Single, validated correlates based on threshold antibody levels, are available for tetanus and diphtheria disease[4]. No agreed threshold for antibody-mediated protection against pertussis disease is available, although antibody against pertussis toxin is generally deemed necessary for protection against severe pertussis disease in naïve infants.

A systematic review conducted by Karla Soares et al. on the absolute reactogenicity of pertussis vaccines compared various vaccines on the outcomes of redness, persistent crying, temperature $\geqslant$38°C, hypotonic, hypo-responsive episode, local pain/tenderness, swelling/nodule, seizures and any other systemic symptoms of aP and wP containing vaccines.

Andy Clark reported on his group's modelling efforts in estimating the direct impact of wP schedules on pertussis deaths among children aged <5years. The aim of these efforts was to use nationally relevant data (vaccine coverage by age, deaths by age as presented

[4] Vaccines, 6th Edition Edited by Stanley Plotkin, Walter Orenstein, and Paul A. Offit. Philadelphia, PA: Elsevier, 2013. 1392 pp.

earlier by Colin Sanderson) to estimate the direct effectiveness of two alternative wP schedules (2p+1 and 3p+0 i.e. a 6, 10 (or 14) and 9 month schedule versus a 6, 10, 14 schedule) on pertussis deaths <5 years. Parameters entering the model derived from national and international data sources: the distribution of pertussis deaths by age in weeks (pre-vaccine era) and the coverage of DTP1, DTP2 and DTP3 and first dose of measles containing vaccine (MCV1) (as a proxy for a 9 month DTP coverage) by age in weeks as well as the vaccine efficacy by dose and the duration of vaccine-induced protection. The focus on mortality was chosen due to the high severity in younger infants which had been consistently observed, irrespective of country. Age distributions of pertussis deaths in the pre-vaccine era were chosen from 2 high income countries (USA and England) as well as 4 low-income countries (Senegal, India, Kenya, South Africa). In addition the national estimates of vaccine coverage and timeliness by dose as presented by Colin Sanderson were fed into the model. The first estimate taken from the model was the number of potential deaths prevented by each dose, based on the pre-vaccine era distribution. The meeting participants provided feed-back that was then used to adjust the modelling of age curves and other parameters used in the model to adjust impact estimates. This report benefits from this revised modeling work completed since the meeting and from the updating of the systematic review of the immunogenicity, effectiveness and reactogenicity of wP vaccination scheduled performed by LSHTM and particularly by Patrick Nguipdop-Djomo and Riya Modley under the leadership of Paul Fine.

Current WHO schedule recommendations and current schedules in use

WHO recommendations on the use of pertussis vaccines

As stated in the 2010 WHO position paper on the use of pertussis vaccines[1], WHO currently recommends a 3-dose primary series, with the first dose administered at age 6 weeks; subsequent doses should be given 4–8 weeks apart, at age 10–14 weeks and 14–18 weeks. It is also recommended that the last dose of the recommended primary series be administered by the age of 6 months. WHO recommends that all infants, including those who are HIV-positive, should be immunized against pertussis.

Considering that the duration of protection following primary immunization varies considerably depending upon factors such as local epidemiology, immunization schedule and choice of vaccine, a booster dose is recommended for children aged 1–6 years, preferably during the second year of life. The stated rationale for this preferred earlier boosting during the second year of life, is that this will improve protection following the primary immunization should a less effective vaccine (wP or aP) be used, thus preventing early accumulation of susceptible individuals. The timing of this booster would also to provide an opportunity for catch-up vaccination and allow for the use of a combination vaccine containing both pertussis and Hib antigens. The booster should be given $\geqslant$6 months after the last primary dose.

Completion of this schedule (primary series plus booster) is expected to ensure protection against pertussis for $\geqslant$6 years i.e. past the period of highest risk for serious pertussis.

Although vaccination can prevent pertussis in adolescents and adults, the WHO position paper states that there is insufficient evidence to support the addition of booster doses in these age groups in order to achieve the primary goal of reducing severe pertussis in infants. Decisions concerning such programmes should be based on both incidence and cost-effectiveness data; embarking on a strategy to vaccinate adolescents and adults

presupposes there is high coverage of routine immunization in infants. Only aP-containing vaccines should be used for vaccination in those aged >6 years.

In the Revised guidance on the choice of pertussis vaccines published in August 2014[2] as a result of the April 2014 SAGE recommendations, it is stated that "available evidence indicates that licensed aP vaccines have lower initial efficacy, faster waning of immunity, and possibly a reduced impact on transmission relative to currently internationally available wP vaccines." This is likely ascribed to the fact that aP vaccines induce a different type of immune response (higher Th2-promoting antibody responses but lower Th1 and Th17 responses), which is less effective at clearing mucosal infections. Individual protection against severe or fatal pertussis in infancy and early childhood is acquired after a primary series of vaccination with either wP or aP vaccine in healthy infants." Based on the SAGE recommendations, WHO advises that "countries where <5 doses of pertussis vaccine (only 3 primary doses, or 3 primary doses plus 1 booster) are used/affordable should continue to use wP vaccines for primary pertussis infant vaccination. " "When considering a switch from wP to aP vaccines, countries need to consider the overall goal of their immunization programme. Disease-related mortality in the first year of life can be significantly reduced using a primary series of either wP or aP vaccination, whereas the protection of older children or adults requires repeated boosting with aP vaccines. "

The revised guidance acknowledged that the main aim of pertussis vaccination was to reduce the risk of severe pertussis including death in infants and young children. All children worldwide should be immunized against pertussis, and every country should seek to achieve early and timely vaccination, initiated >= 6 weeks and no later than at 8 weeks of age, and maintain high levels of coverage (⩾90%) with at least 3 doses of assured quality pertussis vaccine.[5]
Individual protection against severe or fatal pertussis in infancy and early childhood is acquired after a primary series of vaccination with either wP or aP vaccine in healthy infants.

Evidence suggests that ⩾90% coverage with effective vaccines leads to high levels of protection in children in the <5 year age group and that any reduction in overall coverage can lead to an increase in cases of pertussis.

Guidance on the prevention of mortality in the very young infants too young to be immunized is not included in this updated guidance document, although it was discussed

[5] Vaccines of assured quality include vaccines produced in a country with a functional national regulatory authority (NRA), including vaccines prequalified by WHO. WHO defines a vaccine of assured quality as one that consistently meets appropriate levels of purity, potency, safety and efficacy, as judged through an independent review system competent to make an evidence-based decision on the product for a specific population in a specific context. Such a review system makes use of all available information, such as licensing dossiers, surveillance of field performance, lot-by-lot scrutiny, appropriate laboratory testing, current Good Manufacturing Practice, inspection of manufacturers, and evaluation of clinical trials. This definition therefore depends on the existence of a competent and functional regulatory authority (NRA) to regulate the product, as assessed by an external expert team using widely agreed indicators. This definition also indicates clear pathways to improve vaccine quality by strengthening national regulatory authorities, which WHO is actively engaged in doing. Only vaccines of assured quality should be considered for use in national immunization programmes.
http://www.who.int/entity/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf?ua=1

by SAGE in April 2014. This guidance will be included in a full updating of the pertussis position paper

Current national immunization schedules

Based on the analysis of the 2014 UNICEF/WHO joint reporting, there are many variations in country specific schedules, with 87 different schedules among the 194 WHO Member States. In addition to this variation, there is much evolution within countries, with changes of schedule from one year to another relatively frequent.

Notwithstanding, the coverage levels achieved with the booster dose(s) which are rarely measured and likely suboptimal in many countries, less than 30% (62/194) of the countries rely only on 3 doses of pertussis vaccine. Many countries offer a booster dose in the second year of life and/or at between the age of 6 and 13 years. The two following tables provide a summary of current schedules broken down by region.

WHO regions (N of countries)		Number of doses for <7 years			>7 years or adult doses	N of countries using aP	**N of countries using ap in primary**
		3	4	5 or more			
AFR	*(47)*	40	7	0	0	2	2
AMR	*(35)*	2	9	24	12	12	6
EMR	*(21)*	5	8	8	2	6	6
EUR	*(53)*	0	35	18	23	42	41
SEAR	*(11)*	6	3	2	0	0	0
WPR	*(27)*	9	13	5	7	13	13
Total	***(194)***	**62**	**75**	**57**	**44**	**75**	**68**

WHO regions (N of countries)		2, 3, 4 months	2, 4, 6 months	6, 10, 14 weeks	other with all 3 doses given <=6M	2+1 schedule	**other**
AFR	*(47)*	2	2	39	4	0	0
AMR	*(35)*	0	29	1	4	0	1
EMR	*(21)*	1	11	6	3	0	0
EUR	*(53)*	10	18	0	15	9	1
SEAR	*(11)*	1	4	6	0	0	0
WPR	*(27)*	2	5	11	9	0	0
Total	***(194)***	**16**	**69**	**63**	**35**	**9**	**2**

The African region (AFR) and the South-East Asian region (SEAR) and low/middle-income countries (LMIC) in Western-Pacific region (WPR) share the DTP schedule of 6, 10 and 14 weeks, without administration of a booster, using the DTwPHibHepB combination vaccine. This vaccine is also used mainly in Eastern Europe as well as low-income countries in the Eastern-Mediterranean region (EMR) and Latin America in a schedule of 2, 3, 4 months and ~18 month booster or 2, 4, 6 with 18 and 60 month boosters, respectively. High income countries in North America, Western Europe and the Pacific Region use the combination DTaPHibIPV vaccine, with or without hepatitis B, with schedules varying from 4 to 6 doses between two and 60 months of age.

The European region (EUR) is currently the only region where the majority of countries use an aP-containing vaccine for primary immunization. In WPR close to 50% of countries (13/27) use aP for primary immunization.

60% of countries use DTwPHibHepB, 12% use DTaPHibIPV, 12% use DTaPHibHepIPV, 3% use DTwP and 5% use DTaP. 8% use a different combination than these that are listed.

In AFR, all but 2 countries (Mauritius and South Africa) use a wP containing vaccine with a booster dose of aP or wP administered in 7 countries.

In the Americas, the primary vaccination schedule is more uniform at 2, 4 and 6 months in most countries and all countries but two (Haiti and Guyana) administer booster doses. All but 5 countries use wP containing vaccines for the primary course and an additional 3 countries use aP for older age groups. Ten countries have introduced TdaP for older age groups.

In EMR, four countries use mixed aP/wP schedules for their primary and/or booster doses, the other countries use a wP containing vaccine. Only one country (Saudi Arabia) uses exclusively aP. The poorest five countries (Afghanistan, Pakistan, Somalia, Sudan, and Yemen), use a three-dose schedule starting at 6 weeks of age without administration of booster doses.

In EUR, there is a lot of variations between country schedules. All countries use boosters and most use aP containing vaccines. Low and middle income countries are mainly using a 4 dose schedule with a booster before two years of age.

In SEAR, only wP containing vaccines are used, and 5 out of 9 countries administer booster doses.

WPR has a mixed picture both in terms of aP or wP use and in terms of schedules and this is related to the income level of countries. About half of the countries use wP, the other use aP vaccines, including China. Eighteen of the 27 countries administer an aP or wP containing booster.

Globally, of the 30 countries with the largest birth cohorts, 22 are exclusively using wP containing vaccines for their primary immunization and 14 of those countries only rely on a 3 dose primary vaccination course.

The combination DTwPHibHepB is the most popular vaccine across all WHO regions used in over 120 countries (60%), followed by DTaPHibIPV and DTaPHibHepIPV which are used predominantly in Europe and the Americas (12% of countries for each) . In addition 3% of countries use DTwP and 5% use DTaP, while 8% use a different combination.

The largest supplier of the DTwPHibHepB is the Serum Institute of India. Over 50 countries use this vaccine exclusively. Other manufacturers' products are used to a much lesser extent.

It is to be noted that the above mentioned information relates to administration of vaccines as part of the national immunization programmes. In some settings, the administration of the vaccine by the private sector, which may be significant, relies on the use of different vaccines and schedules.

Further all the above relates to the recommended age for vaccination and not to the actual age of vaccination and delays in vaccination are experienced for DTP1-3.

More specific information can be found in the LSHTM report.

In conclusion, there was a great variation in the schedules used globally with more consistency noted in relation to income (Higher income = 3p+1, DTaPHibIPV; Lower income = p3+0 or p3+1, DTwPHibHepB). All countries using aP employed a booster 1-6yrs. The specific product most widely included in national programmes is the pentavalent combination DTwPHibHepB vaccine manufactured by the Serum Institute of India.

Framing of the policy questions

The main incentives for countries to change the schedule would be an increase in vaccine impact in line with a greater control of the specific disease or reduced costs of the program (i.e. ideally by reducing the total number of doses administered or the administration cost per dose).

The pertussis working group and invited experts first discussed the specific criteria to be taken into consideration for specific vaccines/ schedules, including the age at first dose and interval between doses and related gains or trade-offs. The following priority/high level criteria to be taken into consideration during the deliberations to inform the policy questions were agreed upon:

- Maternal antibodies (conferring initial protection / interfering with early infant responses)
- Pertussis- diphtheria –tetanus epidemiology and particularly the epidemiology of pertussis in young infants
- Disease control objectives for all three diseases
- Coverage (at a given age)
- Regulatory approval of the vaccine
- Correlates of protection (circulating antibodies, memory, intervals between priming and boosting)
- Degree and duration of protection
- Reactogenicity in infants when spacing primary doses and booster
- Safety
- Potential co-administration of other vaccines (Hib, Hep B, IPV)
- Availability /licensed vaccines and licensing conditions
- Number of contacts/ number of shots per visit
- Number of doses needed with a specific schedule.
- How criteria differ for wP vs aP-based vaccines
- Cost-effectiveness
- Costs of changing schedules

The stated key policy questions were:

> Is there enough evidence to support the preferential use of different DTP-(X) immunization schedules?
> How does this differ for wP and aP-based vaccines?
>
> Is there enough evidence to identify criteria supporting the preferential use of different DTP- (X) immunization schedules?

Current schedules in use to be considered and then selected/ dismissed by the working group based on the available/not-available evidence included the following:

Age at first dose:

- 6 weeks
- 8 weeks
- 12 weeks and onwards

Number and timing of primary infant doses

- 3 doses using an accelerated schedule (6-10-14 weeks or 2-3-4 months)
- 3 doses using an extended schedule (2-4-6 months)
- 2 doses using an extended schedule (2-4 months and 3-5 months)
- 2 doses using an accelerated schedule (2-3months and 3-4months)

Infant-toddler booster

- None
- <9 months
- 9-11 months
- 12-14 months
- ≥15 months

Preschool booster

- None
- < 4years
- 4-5 years
- ≥6 years

Epidemiology of pertussis, diphtheria and tetanus

Age distribution of pertussis in the pre and post vaccine area

The discussions of the working group evolved around the presented figures, noting there were some for which only very few time points were available. The working group agreed that pertussis mortality would be seen only at 7 days minimum post-birth. The group also agreed that each age distribution curve should normally have only one peak and that a two peak distribution like that shown for Kenya would be more likely to be an artefact of the limited data in the context of an extended tail of the age distribution.

The importance of the case-definition and diagnostic tests used, which may differ throughout countries, was flagged. It was questioned whether the evidence was

sufficient to demonstrate disparity between the countries is attributable to the different schedules used in the countries. Unfortunately the data do not supply information on these disparities.

Limited data on the distribution of recognised pertussis in unvaccinated (pre-vaccine) populations indicate that most individuals were infected in childhood, with > 50 %, exhibiting classical disease. Approximately 80% cases occurred in children under 5 years in some parts of the USA, and less than 3% cases in persons aged 15 years or above (Fales 1928). This was based on typical clinical cases and in the absence of laboratory diagnosis. Similar patterns were observed in other countries, including in Africa and South Asia. Case fatality rates were high, in particular in infancy.

For the developing country-specific patterns of the pre-vaccine era appreciable mortality was reported also in older age-groups whereas in the US and England and Wales, most deaths occurred in the younger age-group. In developed countries the case fatality in younger age-groups was higher than in older age groups.

The introduction of effective infant vaccination with high coverage was accompanied by a steep decline in the number of pertussis cases and deaths in children worldwide, and a shift in the age distribution of pertussis to older ages, in particular in industrialized countries. The age shifts may, in part, be explained by an increasing awareness and recognition of the less typical disease manifestations in older subjects, as well as more sensitive surveillance and laboratory testing, and surveillance covering the entire life span, not only in children. Waning of the infant vaccine-derived immunity, combined with lower naturally-acquired immunity and boosting (as a result of lower community transmission rates) is likely to play a role in increased susceptibility in adolescents and adults.

Specific age distribution graphs are provided in the LSHTM companion document.

In conclusion, the prevention of infant pertussis is a key driver requiring DPT immunization to be initiated as early in life as possible.

Age distribution of diphtheria in the pre and post vaccine area

Prior to the introduction of diphtheria antitoxin and its widespread use, and to the development of diphtheria toxoid vaccines in the 1920s, diphtheria was widespread in most countries in Europe and in the USA and Canada. However, around the mid-1940s, many countries started to report rapid declines in notifications. Diphtheria declined to near elimination by 1980 when globally 97,164 cases were reported from all WHO regions. But beginning in the late 1980s, massive outbreaks occurred in the Russian Federation and newly independent states. In 2013, about 67% of 4679 cases were reported from India. Overall there has been a steady decline in the number of reported diphtheria cases to the WHO from 1980 to 2013 by every country (except the years of the Russian Federation epidemic). Diphtheria is now exceptional in many of the industrialized countries. The vast majority of cases in the industrialized countries represent importations from other countries where diphtheria transmission is still occurring.

From 1990 to 1997, a total of 115,088 cases of diphtheria were reported in Russia and Newly Independent States, including 3078 fatalities. During this period, 27–32% of the annually reported cases occurred among children (<14 years); 6–8% among adolescents

(14–17 years), and 58–68% in adults (18–19, and 40–49 years). Of 99,861 cases seen at the Gabrichevsky Institute, Moscow during this period, 32% of cases were in individuals aged <15 years old. Despite this massive outbreak, few related cases, exclusively among adults, were reported from other neighboring European countries (including the Netherlands, Belgium, Germany, Finland, Greece, and the United Kingdom) during this period.

A few other relatively small outbreaks have occurred in the past decade in countries such as Afghanistan, Ecuador, Paraguay, Haiti, Dominican Republic, Indonesia, Lao and Nigeria predominantly in children <14 years and most cases occurring in unvaccinated individuals. An outbreak of diphtheria in Thailand in 2012 revealed an unusual pattern, with most cases being 5-14 and 20-44 years of age. This age-grouping could be explained by changes in the schedule over time, and by cohorts 20-44 years having received less doses whereas in the younger group the outbreak mostly affected Hmong communities where vaccine acceptance is low.

Interpretation of data needs to be done with caution. Although WHO has a standard case definition, this is not uniformly implemented across WHO regions and countries. As no standard case-definition is implemented and it is unclear whether confirmed or clinical cases only are reported. It is further uncertain what is reported as a case of diphtheria (all types, carriers, close contacts) and toxic vs non-toxic *C. diphtheria.*

The underlying cause of the outbreaks was questioned, in particular for cases in mid-adulthood, (except the one occurring in the Russian Federation) i.e. in Yemen and Jordan i.e. was it a lack of booster doses or a lack in coverage? The overarching question being: Does diphtheria only occur in unimmunized?

The discussions of the working group evolved around the possible environmental burden, the waning of immunity, and the immunization coverage. The working group concluded that with circulation of the disease, in most cases, despite low diphtheria antibody levels in adults outbreaks of diphtheria do not occur. One probable explanation for the discrepancy between serological findings of low antibody levels at distance of the last booster and the rarity of cases in previously immunized individuals is that protection still persists despite undetectable levels of antibodies (or below the threshold considered for protection). The risk of acquiring diphtheria is hence not an issue at the population level but rather at an individual level.

Immunization protects against mortality but immunized individuals do acquire and transmit the disease. Maintaining high levels of antibodies, especially among children who are the vectors/amplifiers of disease, is crucial to protect against transmission and disease.

Both during the Russian Federation outbreak as well as the Indonesia outbreak government vaccination coverage rates were reported to be high, though a case-control study revealed that the coverage rates were very low for the cases.

Diphtheria would not be the main driver for the DTP schedule. The data demonstrated that the disease is well-controlled even if no booster is applied. There might not be individual-level protection but disease control was ensured with the current schedules, even if not including boosters.

In conclusion, the incidence of diphtheria was high in the pre-vaccine era in many countries and it affected young children but spared very young infants. With the introduction of routine childhood immunization in many industrialized countries during the late 1940s, diphtheria notifications steadily declined to record lows in 2012. Although immunity wanes over time, serologic studies show an expanding protective immunity to older age groups, most likely related to a greater Td coverage. Unfortunately, recent outbreaks in populations with low vaccination coverage were observed which mainly affected children <15 years of age.
In industrialized countries sporadic cases occur in older individuals mainly related to importations of diphtheria disease, e.g. in Australia.
The prevention of diphtheria does not require immunization to be initiated very early in infancy, nor repeat boosters, but to achieve a high coverage through infant immunization.

Age distribution of tetanus in the pre and post vaccine area

Data are very limited as surveillance is generally passive and even higher income country systems capture only 20-60% of the cases. In many LMIC, non-neonatal tetanus (nNT) is not notifiable and under-reporting is common.

nNT is defined as tetanus occurring at 29 days of age or older. Over half of nNT cases (47-82%) are associated with acute wounds, most commonly punctures and lacerations, but also including abrasions, burns and excoriations. nNT also is associated with a wide variety of non-traumatic conditions. Up to 30% of tetanus cases in published series have no known associated cause.

In the pre-vaccine era, the burden of nNT was as unclear as that of NT. Modeled estimates suggest that as many as 500,000 nNT cases occurred annually in the 1980s. 50-70% of nNT cases occurred in children who also had the highest age-specific incidence of the disease. Starting around 5 years of age, the number and incidence of cases in boys tended to be greater than those for girls.

In higher income (industrialized) countries, tetanus was relatively rare even before tetanus toxoid-containing vaccines (TTCV) were introduced. Incidence and mortality had slowly declined in association with urbanization, higher living standards, modern concepts of hygiene and other factors unrelated to vaccination.

The highest burden of tetanus in the pre-vaccine era occurred in neonates followed by children $\leqslant$15 years of age. After introduction of DTP in infancy, the incidence of paediatric tetanus has declined, as has NT and tetanus in adult women in association with TT administered to women of reproductive age (WRA). In countries where DTP and TTCV boosters have been in use for decades, an upward age shift in numbers and rates of nNT has been observed and tetanus has become increasingly rare. The upward age shift has been less striking in countries where only infants and women of reproductive age are targeted for vaccination with TTCV, however high coverage with the primary series was achieved only relatively recently in such countries. Pediatric tetanus (cases in children< 15 years) is very rare and usually occurs in unvaccinated children. The numbers of cases, incidence and mortality are all highest in older adults. Current susceptibility to tetanus (not being addressed by the maternal and neonatal tetanus elimination (MNTE) program is in

those who are inadequately immunized with TTCV, mainly adolescents and adult males in LMIC.

No new evidence was presented that would challenge the current evidence presented in the WHO Immunological Basis of Immunization series - Module 3: Tetanus Update 2006 and Module 2: Diphtheria update 2009 (available on the SAGE website) .

Vaccine immunogenicity, efficacy and effectiveness including of alternative and reduced schedules

Diphtheria and tetanus containing vaccines

Number of doses

Five studies compared 2 vs. 3 primary doses. Outcomes were assessed with low or very low level of evidence (limitations, imprecision; but includes evaluations on correlate of protection), suggesting that for both diphtheria and tetanus, 2 doses resulted in substantially lower antitoxin mean titers (factor down to 0.5) than three doses, one to seven months post primary vaccination. Data at one month after a booster dose are inconsistent for diphtheria, with 1 of 2 studies reporting lower titers for diphtheria and little or no difference for tetanus. Differences did not translate into a substantially decreased prevalence of putatively protective or otherwise dichotomized antitoxin levels.
Appropriate not-per-protocol studies supported lower antitoxin titers after 2 compared to 3 doses soon after the primary series, and, for diphtheria, at age 3 years.
Among children aged 0-2 years during a diphtheria outbreak, the results suggest that vaccine effectiveness is >90% for one, two or three primary diphtheria doses given during the first 12 months of life; and among children aged 3-5 years, vaccine effectiveness >90% for two or three primary doses, or ≥99% after a fourth dose at age 2 years. Tetanus toxoid neutralizing titers were 20-fold higher one month after a 2nd dose in 6-mo interval, compared to no vaccination. Previous reviews provide further evidence[6], that 1 dose does not confer significant protection against DT but 2 doses result in protective titers in close to 100% in infants. Even higher titers and longer duration can be elicited following 3 doses.

Age at primary vaccination

Two studies on birth dose and two on other schedules addressed the effect of age at initiation of vaccination. A birth dose prior to a 2, 4, 6 month schedule did not provide higher antitoxin GMC against diphtheria or tetanus between age 6 through 9 months or after a booster in the second year or life(*Very low level of evidence*).Furthermore, one study suggested that 3, 4, 5 vs. 2, 3, 4 month schedule provides similar antitoxin seroprevalence above a threshold of 0.01 IU/ml (ELISA) or GMC against diphtheria and tetanus, at one month post third primary or booster dose (*Low level of evidence*: indirect evidence as not using putatively protective levels, only one moderately large study). A single study suggested that initiation of vaccination with 3 primary doses at age 9-23 months compared to age 3-8 months does not provide higher antitoxin titers against diphtheria or tetanus (assay not per protocol) (*Very low level of evidence:* cohort with limitations, indirectness, imprecision). Appropriate not-per-protocol studies support the absence of a substantial effect from age at primary series initiation.

[6] Orenstein WA, et al.Diphtheria and tetanus toxoids and pertussis vaccine, combined. In: Recent advances in immunization: a bibliographic review. Scientific pub no. 451. Washington: PAHO, 1983:30-51.

Intervals between doses
Three immunogenicity studies addressed the effect of length of interval on the outcomes with an overall very low level of evidence (limitations, indirectness, imprecision). Results suggest that an accelerated schedule results in lower level of antibodies (factor 0.5) after the third dose or during the second year of life, when compared to a schedule with an interval of around 6 months between 2nd and 3rd doses. One appropriate not-per-protocol study is compatible with higher antitoxin titers after accelerated schedule which is different from other available data. Higher D and T titers were observed after a 2 versus 1 month interval though no difference was found 1 year later.

Two studies with overall very low level of evidence (one single case control study with low sample size and large confidence intervals per number of doses; one small clinical trial with unclear allocation procedure) addressed the effect of any vaccination on the outcomes.

Impacts of boosters
The effect of any booster vaccination on the outcomes was addressed by one study, with overall very low level evidence (one single small RCT with unclear limitations, indirectness). The result suggests substantial increase in diphtheria and tetanus antibody due to booster vaccination at 18 months, following an initial 3, 4, 5 month schedule. The results suggest that delaying booster vaccination against diphtheria or tetanus to age 18 months, compared to 12 or 15 months, may yield higher antitoxin concentrations, while the differences likely do not translate into higher prevalence of putatively protective concentrations.

Overall very low level of evidence as most studies were relatively small, each question was addressed by only one or two studies, the outcomes (mean titers per group) were mainly indirect and the studies showed risk of biases (design, blinding, confounding).

With respect to the minimal interval between priming and booster doses it was noted that there were no data on intervals shorter than 6 months. Additional research on the minimal interval would be needed if shorter intervals were to be recommended.

In conclusion, there is some evidence available for all questions on DT primary or booster schedules, with limited level of confidence. Only one study evaluated vaccine effectiveness (VE).
- Concerning 2 vs. 3 primary doses there was a substantially lower mean antitoxin titer after primary series, but the difference did not persist during the 2nd year of life (rapid antibody decline regardless of the number of primary doses) and after boosting and did not clearly translate into a difference in clinical protection *(overall low quality of evidence[7]).*
- A long interval (6 months) between 2nd and 3rd dose provides substantially higher antitoxin titers for the 2nd year of life (*very low quality of evidence*).
- The birth dose (in addition to a 3-dose primary series) does not provide higher antitoxin titers (*very low quality of evidence*).

[7] GRADE level 1 indicates very low quality of evidence, GRADE level 2 indicates low quality of evidence, GRADE level 3 indicates moderate quality of evidence, GRADE level 4 indicates high quality of evidence (http://www.gradeworkinggroup.org/)

-The age of initiation of a 3-dose primary series does not substantially impact on resulting antitoxin titer levels, (*very low quality of evidence*).
- Booster vaccination at age 18 months yields slightly higher antitoxin concentrations than earlier boosting, but does not offer better protection, (*low quality evidence*).
Booster vaccination during the 2nd year of life after a 3-dose primary series substantially increases antitoxin titers.

Pertussis containing vaccines (wP and aP)

Whole cell pertussis vaccines (wP)

This section only presents summary information as extracted and copied from the companion LSHTM document on the wP vaccine schedules. Much more detailed and contextualized information appears in this document.

Immunogenicity data are difficult to interpret and compare for whole-cell Pertussis vaccines. There is no established immunological correlate of protection against pertussis disease[8], although PT is believed to play a critical role in protection against severe infant disease. Different wP vaccines may have different antigenic content and ways of production and controls, leading to variations in post-vaccination immune response. There are limited data in the literature, and much of the available information refers to vaccine formulations no longer in use. However, patterns of immune response may contribute insights on vaccine effectiveness.

Limited evidence from a systematic review[9] suggest that the short-term immune response (few weeks to months post-vaccination) increases with the number of doses, and appears to be stronger with longer intervals between primary doses. Observational studies report higher antibody titres 6-8 weeks following the 3rd dose when given after ~ 6 months [i.e. (2+1)p schedule] than when given 1-2 months after the 2nd dose (i.e. 3p schedule).

With respect to vaccine effectiveness by schedule, there is:

- Moderate quality evidence (including 4 controlled trials and 3 screening and 3 case-control studies) that 3p schedules are effective against pertussis disease in the first 5 years of life.
- Low grade evidence (no data from RCTs) that (2+1)p schedules are effective against pertussis at age 1-5 years (protection in under 1year old not included). Limited data on VE of 2 doses in infants under 1years old.
- Very limited data on direct comparison of 3p and (2+1)p schedules; no direct evidence that either schedule is superior or inferior to the other.

Effect on vaccine effectiveness of interval between 1st and 2nd dose:

- No within-study data available. Limited evidence from between-study comparisons that VE is no different with 3p at monthly or 2-monthly intervals
- No data on interval other than 2-monthly between 1st and 2nd doses for (2+1)p

[8] Wirsing von König C. *Module 4: Pertussis*. Geneva: World Health Organization; 2009. Available at: http://whqlibdoc.who.int/publications/2010/9789241599337_eng.pdf

[9] Mueller J, Koutangni T. Comparative efficacy/ effectiveness of schedules in infant immunization against pertussis, diphtheria and tetanus: Systematic review and meta-analysis. Part 2: Whole-cell pertussis vaccine. Unpublished report to WHO. August 2014. (available on the SAGE website)

Age at initiation of first dose and Vaccine effectiveness:

- Data on effectiveness are only available for schedules initiated around 2-3 months, not earlier.
- There is no within study comparison of VE of similar regimens starting at 2 months versus later age. Between-study comparisons provide no evidence on whether wP vaccine efficacy is different when the 1st dose is given at 2 or 3 months.
- There is low grade evidence (1 small RCT) that antibody response to a primary vaccination course is similar whether or not an additional dose is given at birth.

Childhood boosters:

- 3p: Very low grade evidence on effect of booster dose in children under 5 years. Limited evidence of benefit.
- (2+1)p: No evidence relating to additional effectiveness of booster dose in children under 5 years

In the companion document information is also presented on vaccine effectiveness and duration of protection.

The literature search did not identify any study that measured wP effectiveness against pertussis death. However, a review of the evidence by the SAGE working group that was presented to SAGE in April 2014 (see Report of the SAGE pertussis working group, March 2014) looked at severe pertussis morbidity and hospitalization in infants less than 1 year of age as a proxy, given that the disease is likely to be more severe or fatal in infants, thus any vaccine-induced protection against severe disease may apply to pertussis death. The following table is extracted from this report and summarizes vaccine effectiveness against infant disease and hospitalization both for aP and wP vaccines.

Country/ Vaccine	Single dose	Two doses	Full primary schedule
Australia aP	VE hospitalization: 55% (95%CI: 43-65%)	VE hospitalization: 83% (95%CI: 70-90%)	VE hospitalization: 85% (95%CI: 75-91%)
England aP or wP	VE against infant pertussis disease: 62% (95%CI: 53-69%)	VE against infant pertussis disease: 85% (95%CI: 77-91%)	VE against infant pertussis disease: 95% (95%CI: 86-99%)
France wP	VE against infant pertussis disease: 58%	VE against infant pertussis disease: 87%	VE after 4 doses against infant pertussis disease: 84%- 100%
Germany aP	VE hospitalization: 68.0% (95%CI: 45.6-81.1)	VE hospitalization: 91.8% (95%CI: 84.7-95.7)	
USA DTaP/ Tdap			VE after 5 doses of DTaP, approx. 98% in first year after vaccination but declining to approx. 75% >5years after vaccination. VE of Tdap: 75% in the first year declining to 40% after 2-4 years.
USA DTwP/DTaP	VE against pertussis disease in ages 6-23mo: 50.5% (95% CI: -71.1-86.3)	VE in ages 6-23mo against pertussis disease: 80.1% (95% CI: 41.3-93.2)	

Based on this in April 2014 SAGE concluded that there is increasing and consistent evidence both from observational and analytical studies from a number of industrialized countries using aP and wP to show that a single dose of either pertussis vaccine in infancy has around 50% effectiveness in preventing severe disease, hospitalization, and death and that 2 doses of either pertussis vaccine offers higher protection (83%-87%).

The group concluded that timely delivery of the first dose as soon as possible after 6 weeks of age is critical, but the age at which the first dose is recommended should depend on the local epidemiology and vaccine delivery system. While on-time vaccination is crucial regardless of the schedule, the group reinforced that 1 or 2 doses are not sufficient and that completion of the entire recommended number of doses is needed to protect older age groups, which might not be at risk of death but still at risk for increased morbidity and who may contribute to transmission of the disease to unvaccinated young infants.

Acellular pertussis vaccines (aP)

For aP vaccines, 33 studies were retrieved by the systematic review (19 RCT and 14 observational) along with 11 not-per-protocol studies (7 RCTs, 2 observational). The section below just focusses on the studies that are informative in relation to the comparative schedule question.

For information on the effectiveness of one versus two doses of vaccine against death please refer to the previous section on wP vaccine and previous discussions from SAGE on this issue. SAGE concluded that evidence is not sufficient to assess a significant difference in vaccine effectiveness using different component aP vaccines; there is no evidence pointing to the superiority of one aP vaccine over another. The systematic review did not add additional robust information on the effectiveness of 1 or 2 doses but was used to generate the upper and lower bounds around the existing effectiveness estimates for the modelling by LSHTM.

The effect of initiation of a 3+1 schedule at 3 vs. 2 month of age was addressed by one RCT (1-month intervals) and one cohort study (2-month intervals). The proportions of seroconverters or Geometric Mean Titers (GMTs) after the 3rd dose or a booster are similar (*Low and moderate quality of evidence*). Delaying the initiation of a 3+1 schedule from 3-8 months to 9-23 months does not substantially increase immunogenicity (*Very low quality of evidence*).

The comparison between accelerated (3+0) and long (2+1) schedules was addressed by three studies (*Very low quality of evidence*). Schedules assessed were 2, 3, 4 months versus 3, 5, 9 months; 2, 4, 6 months versus 3, 5, 11 months) and 2, 4, 6 months versus 3, 5, 12 months. Only one study using the latter comparative schedule[10] looked at clinical effectiveness. This latter study indicated a lower risk of pertussis from 9 months after the first dose with the 3, 5, 12 months than the 2, 4, 6 month schedule indicating that this extended schedule with a late 3rd dose (acting as a booster) provides better clinical protection after the first year than one without a booster. No comparative efficacy data

[10] Olin P et al. Measuring protection: a case study of pertussis vaccines – Swedish Trial II: secondary non randomized comparisons between two schedules of infant vaccination. Develop Biol Standard 1998:95211-20.

were available for other schedules considered by the working group (WG). In the immunogenicity study comparing 2, 4, 6 months versus 3, 5, 11 months antibody responses were higher at 7 months of age in the former group who had received 3 doses than in the 3, 5, 11 months group who had received only 2 doses by this age. Post dose 3 antibody responses were higher to two pertussis antigens in the 3, 5, 11 months than in the 2, 4,6 month group. In the immunogenicity study comparing 2, 3, 4 months and 3, 5, 9 months antibody levels after 3 doses in the accelerated schedule were similar to those after 2 doses in the extended schedule with no consistent differences between schedules after the third dose.

The comparison of 1-mo versus 2-mo intervals within a 3-dose primary schedule was addressed by 2 studies (*Very low quality of evidence).* The proportion of seroconverters and GMT are similar one month after the third dose. Of note is that the shorter schedule in one study implied later initiation.

The effect of any vaccination on outcomes was addressed by in total 13 studies on clinical efficacy/ effectiveness and 2 studies on immunogenicity.

Across various study designs, schedules and outcome definitions, absolute VE of 3 doses (3+0 or 2+1) is 59-95% (*Moderate to high quality of evidence*) and of 2 doses, 35-86% (*High quality of evidence*). The lower bound refers to a 2 component vaccine that did not proceed to licensure.

Using 3-dose schedules, VE tended to be lower in randomized studies (60-85%) than in purely observational (excluding unblinded RCT) studies (83-95%). In a single RCT using the old WHO definition and studying children <3years of age, a 1-component vaccine used in a 3, 5, 12 month schedule had slightly lower VE (95%CI 71-73%) than a 3-component vaccine used in a 2, 4, 6 month schedule (95%CI 78-84%).

Titers against included antigens after 3 primary doses of any vaccine compared to no vaccination are at least 50-fold higher one month after primary schedule and 4-fold higher 15 months later (*Moderate quality of evidence*).

The effect of booster schedule on the immunogenicity outcomes was addressed by one study (*Moderate quality of evidence*). After a 3-dose primary series before age 8 months, timing of booster between age 15 and 18 months did not result in consistent or significant differences in immunogenicity.

The effect of any booster vaccination on the outcomes was addressed by one RCT (*Moderate quality of evidence*).

A previous review[11] deemed all tested pertussis vaccines efficacious. No data on 2- vs. 3-dose schedules at six months (GMT data or seropositivity) are available. Due to high levels of heterogeneity, summary statistics for efficacy of aP vaccines derived from meta-analysis were not appropriate[12] (only RCTs included).

[11] Jefferson T. Systematic review of the effects of pertussis vaccines in children. *Vaccine*. 2003;21(17-18):2003-2014. doi:10.1016/s0264-410x(02)00770-3.

[12] Zhang L et al. Acellular vaccines for preventing whooping cough in children. Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD001478. DOI: 10.1002/14651858.CD001478.pub5.

In summary:

- 2 vs. 3 primary doses possibly result in substantially lower clinical protection and titers during 1st year of life, until the 3rd dose is given *(Very low to low quality of evidence).*

- 2+1 provides better clinical protection than 3+0 from 3rd dose on, unclear difference before this dose. No meaningful difference in immunogenicity. (*Very low quality of evidence*)

- The age of initiation and length of intervals of 3-dose primary schedule do not substantially impact on immunogenicity *(Very low to moderate quality of evidence).*

- There are inconsistent findings and variability of study design on relative immunogenicity of birth dose (before 3-dose primary series) *(Low to moderate quality of evidence).*

- No serological impact of timing of booster between 15 and 18 months (after 3 primary doses) was observed (*Moderate quality of evidence*)

Of particular relevance is that good level of control of severe pertussis in children and good individual protection was achieved in different countries using different aP primary schedules (i.e. different starting age, different interval between doses as well as different number of doses i.e. 2+1 versus 3 doses and different timing of booster doses). However, a resurgence of pertussis was observed in some countries a number of years after the switch from wP to aP (Australia, Portugal ,USA, UK) leading to an increased risk in unprotected infants including in those too young to be immumized[3]. Countries experiencing a resurgence had used different schedules to each other.

Reactogenicity of pertussis containing vaccines in children with focus on comparative reactogenicity for different schedules

DTwP: There is limited evidence that the risk of adverse events after the third vaccine dose is higher in children using the (2+1)p schedule than those using a 3p schedule. There may be quite large differences between different wP products. More detailed information is provided in the LSHTM report.

DTaP accelerated schedule vs. DTaP long schedule
Three RCTs, two of low[13] [14], one of moderate risk of bias [15]; and two cohort studies, one of moderate[16] and one of moderate-high risk of bias[17] , conducted in Europe, the Middle East and East Asia were included. Mostly, there were no significant differences in reactogenicity between the accelerated and longer DTaP schedules. For some of the time

[13] Li R et al, Immunogenicity and safety of a pentavalent acellular pertussis combined vaccine including diphtheria, tetanus, inactivated poliovirus and conjugated *Haemophilus influenzae* type b polysaccharide for primary vaccination at 2, 3, 4 or 3, 4, 5 months of age in infants in China *Vaccine*. 2011;29(10):1913-1920. doi:10.1016/j.vaccine.2010.12.103.

[14] Hoppenbrouwers K et al. Priming effect, immunogenicity and safety of an *Haemophilus influenzae* type b-tetanus toxoid conjugate (PRP-T) and diphtheria-tetanus-acellular pertussis (DTaP) combination vaccine administered to infants in Belgium and Turkey. *Vaccine*. 1999;17(7-8):875-886. doi:10.1016/s0264-410x(98)00273-4.

[15] Carlsson R et al, Safety and immunogenicity of a combined diphtheria-tetanus-acellular pertussis-inactivated polio vaccine-*Haemophilus influenzae* type b vaccine administered at 2-4-6-13 or 3-5-12 months of age. *The Pediatric Infectious Disease Journal*. 1998;17(11):1026-1033. doi:10.1097/00006454-199811000-00013.

[16] Kamiya H. Immunogenicity and Reactogenicity of Takeda Acellular Pertussis-Component Diphtheria-Tetanus-Pertussis Vaccine in 2- and 3-Month-Old Children in Japan. *Archives of Pediatrics & Adolescent Medicine*. 1992;146(10):1141. doi:10.1001/archpedi.1992.02160220027015.

[17] Acellular vaccines may enhance spread of whooping cough. *Reactions Weekly*. 2013;1482(1):1-1. doi:10.1007/s40278-013-7676-4.

points for erythema/redness, swelling/nodule, any systemic symptoms, and irritability there was a lower risk of adverse events with the accelerated schedule.

There were no significant differences in reactogenicity between the accelerated and longer (DTwP or DTaP) schedules.

Using modelling to explore the impact of different strategies in different epidemiological settings

This section presents the revised estimated resulting from the further work by A. Clark following the August 2014 meeting of the pertussis Working Group

The modelling efforts focused in estimating the direct effectiveness of wP schedules on pertussis deaths <5years. Aim of these efforts was to use nationally relevant data to estimate the direct effectiveness of two alternative wP schedules (2p+1 and 3p+0) on pertussis deaths <5years. The focus on wP was justified by the fact that current WHO recommendations are that developing countries continue with wP for the primary vaccination series and that developing countries have most of the mortality burden from pertussis.

Parameters entering the model derived from national and international data sources: the distribution of pertussis deaths by age in weeks (pre-vaccine era) and the coverage of DTP1, DTP2 and DTP3 and first dose of measles containing vaccine (MCV1) (as a proxy for the DTP booster) by age in weeks as well as the vaccine efficacy by dose and the duration of vaccine-induced protection.

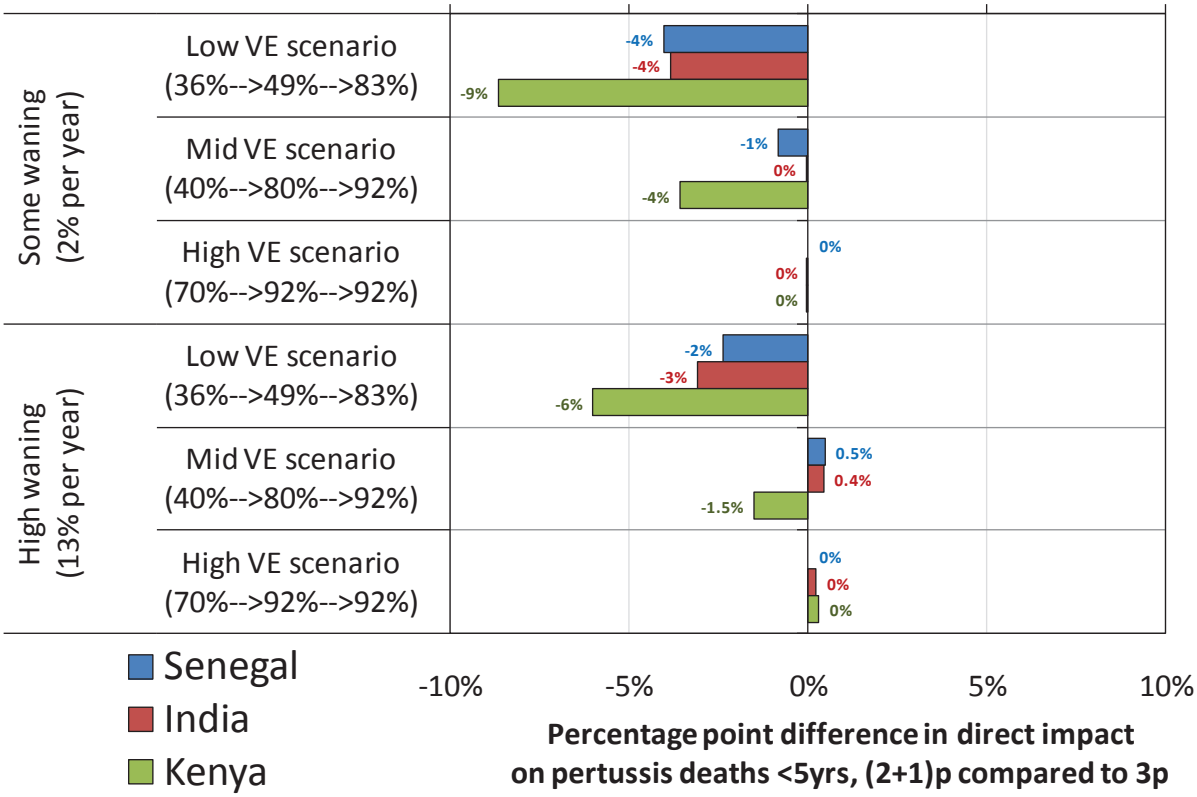
A modelling approach previously used to inform optimal schedules for Hib vaccination [18] was used to infer simple estimates of the benefits of alternative wP vaccination schedules in selected LMICs, namely India, Kenya and Senegal. The 3p (6, 10,14w) schedule currently used in all three countries was compared to two alternative (2+1)p schedules, 6w,10w,9m and 6w,14w,9m. The 9m option was evaluated because all three countries currently administer the first dose of measles vaccine at this age, and data are available on the coverage and timeliness of this visit. The modeled outcome was the direct impact of wP vaccination, defined as the predicted percent reduction in all pertussis deaths <5 years, accounting for the coverage, effectiveness and duration of vaccine-induced protection among wP vaccine recipients. Pertussis deaths were the modelled outcome of interest since mortality reduction is the main priority for pertussis vaccination schedules in LMICs. Herd immunity considerations were not included in these estimates because the available data from these settings is of insufficient quality to accurately capture the age-specific incidence of infection, duration of natural protection, wP vaccine effectiveness vs natural infection, social contact patterns etc. More detailed information on the parameters used for the modelling work is provided in the companion LSHTM paper.

Figure 1 shows the percentage point difference in direct impact of 6w-10w-9m schedule compared to the current 6-10-14w schedule used in India, Kenya and Senegal. The direct impact of the 3p schedule is subtracted from the direct impact of the (2+1)p schedule to estimate the absolute difference in direct impact. Thus, positive differences indicate better direct impact with the (2+1)p schedule. Negative differences indicate better direct

[18] *Haemophilus influenza* type b vaccination position paper – July 2013 Wkly Epid Rec 2013;88:413-428.

impact with the current 3p schedule. A low VE scenario would favor the existing 6-10-14w schedule in all countries. A 6w,10w,9m schedule is slightly favored only if the second dose VE is high (>80%) **and** if protection wanes rapidly. There are subtle differences between the three countries, which reflects differences in the age distribution of deaths (earlier in India) and differences in the coverage of each dose (higher and more timely in Kenya and Senegal), highlighting the need to account for local circumstances where possible.

Figure 1: Percentage point difference* in direct impact vs pertussis deaths <5yrs: (2+1)p compared to 3p in Senegal, India and Kenya



* Note. The direct impact of the 3p schedule is subtracted from the direct impact of the (2+1)p schedule to estimate the absolute (percentage point) difference in direct impact. Thus, positive differences indicate better direct impact with a (2+1)p schedule. Negative differences indicate better direct impact with the current 3p schedule.

A number of additional scenarios were also evaluated (Figure 2):

i. Firstly, given the small numbers involved in fitting the age distributions in India, Kenya and Senegal, a conservative scenario was run based on the pre-vaccine era age distribution in the USA[19]. This was the most heavily skewed distribution to younger ages of all the pre-vaccine era distributions identified in the review. In this scenario, labeled '6w, 10w, 9m (age shifted left)' there was limited advantage of the 6w, 10w, 9m schedule, even under assumptions of high VE and rapid waning;

ii. Secondly, it has been postulated that changing the schedule from 6, 10, 14w to 6w, 10w, 9m could adversely affect the coverage and timeliness of the existing 10w dose. If the timeliness and coverage were assumed to be similar to the 14w dose, only shifted 4 weeks earlier, then there would be a detrimental effect of changing to the 6w,10w,9m schedule – see scenario labeled '6w, 10w, 9m (10w coverage / timing worsens)';

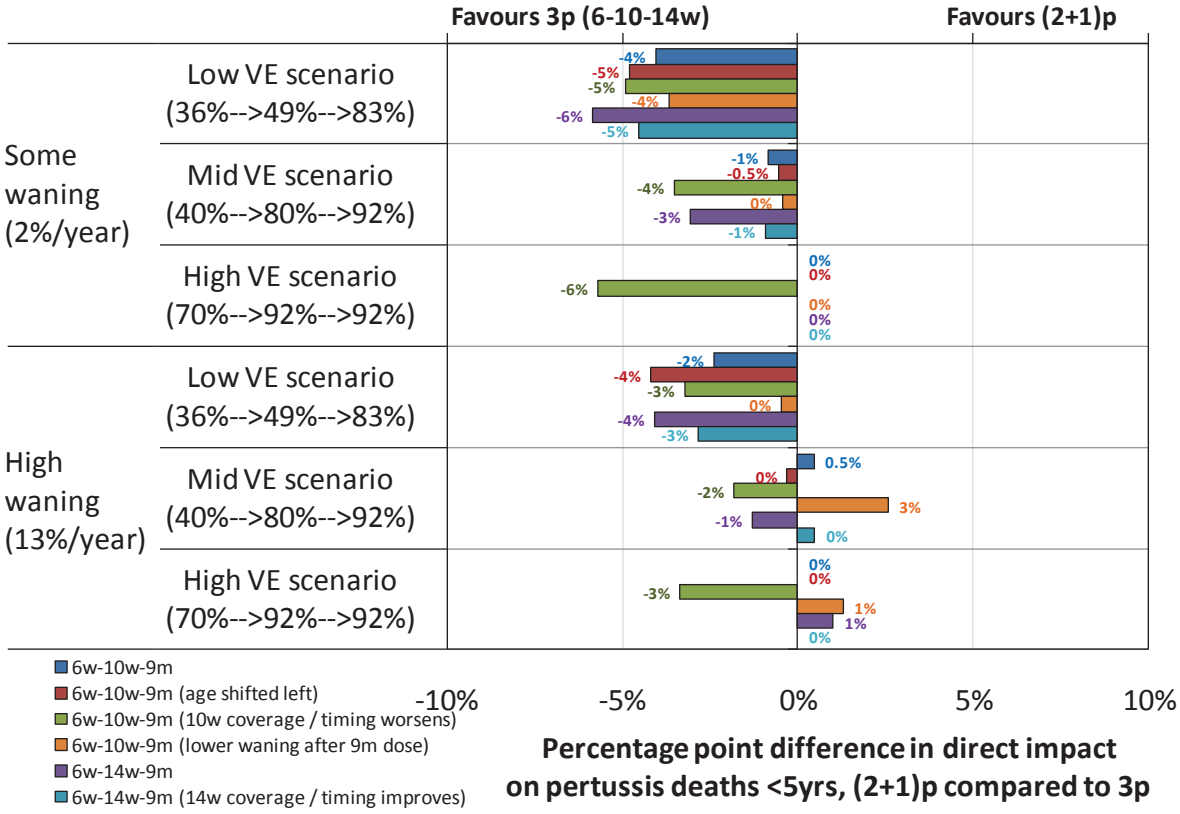
[19] Sako W. Early immunization against pertussis with alum precipitated vaccine. *Journal of the American Medical Association*. 1945;127(7):379. doi:10.1001/jama.1945.02860070011004.

iii. Thirdly, one of the main reasons to delay the 3rd primary dose is to achieve a more durable immune response, and thus less waning. If a 25% lower waning rate were to be assumed after the 9m dose (vs the doses administered at 6,14w) then the 6w,10w,9m schedule would generally be preferable to the 6,10,14w schedule if 2 dose VE is high and waning is rapid – see scenario labeled '6w,10w,9m (lower waning after 9m dose)'. However, there is currently no evidence to support such an advantage, and indeed limited evidence that waning clinical protection occurs irrespective of whether a 3p or (2+1)p schedule is used ;

iv. Fourthly, a 6w,14w,9m schedule was evaluated. This schedule generally had lower estimated direct impact than the 6w, 10w, 9m option because the 14w visit has worse coverage and timeliness than the 10w visit. However, with high VE and rapid waning this option could be slightly preferable to the 6w,10w,9m option; and,

v. Finally, the 6w, 14w, 9m schedule was run under the assumption that timing and coverage of the 14w visit could be improved to reflect the coverage and timing of the 10w visit, labeled '6w, 14w, 9m (14w timing / coverage improves)'. In this scenario there was limited difference between the 6w,10w,9m schedule and the 6w, 14w, 9m schedule. Thus, the 6w,14w,9m option is unlikely to be a practical alternative to the current 6w, 10w, 14w schedule unless: a) there are substantial improvements in the coverage and timeliness of the 14w visit; and/or, b) there is a very significant clinical advantage of increasing the interval from 4 to 8 weeks. There is currently very limited evidence to support either of these assumptions.

Figure 2. Percentage point difference* in direct impact vs pertussis deaths <5yrs: (2+1)p compared to 3p in Senegal – alternative scenarios



In conclusion, there are large uncertainties around highly influential parameters included in the model (e.g. the rate of waning clinical protection) as well as uncertainties about the potential role of parameters that were not included (e.g. herd effects). In most scenarios which assume at least 80% protection after the 2nd dose (the midpoint assumed in this evaluation), a 6w,10w,9m schedule is

likely to achieve similar direct impact to the existing 6, 10, 14w schedule. Thus, current evidence is not strong enough to preclude a move to a 6w, 10w, 9m schedule should this be advantageous for other antigens administered as part of the same combined vaccine. However, moving to a 6w, 10w, 9m schedule could be detrimental if 10w coverage and timeliness are adversely affected. Finally, 6w,14w,9m is likely to be inferior to 6w, 10w, 9m unless dramatic improvements can be achieved in the coverage and timing of the current 14w dose visit.

Conclusions and recommendations

The following summarizes the working group's considerations on the available evidence for each previously framed question. Working group members first reflected on the available evidence in support/against DTwP/DTaP schedules and the evidence on timing of booster doses (aP and wP) before moving to the deliberations on the conclusions and recommendations.

Evidence to support/prevent the use of following DTwP schedules:

Age at first dose
Should be as early as possible ≥6 weeks, thus late schedules not considered further.

2p+0 primary schedule at 6,10 weeks/ 6,14 weeks
No evidence supporting either schedule without additional doses

2p+1 primary schedule at 6,10 weeks plus infant booster (<1 year)
No clinical data from LMIC
Concerns that this schedule would create a window of vulnerability for pertussis between the 2nd dose and the booster as seen in the UK when a 3, 5, 10 month schedule was used before the change to a 2,3,4 months schedule .

2p+1 primary schedule at 6, 14 weeks plus toddler booster
Lower responses against T and D until boosting
Concerns that this schedule would create a window of vulnerability for pertussis between the 2nd dose and the booster

3+0 primary schedule at 6, 10, 14 weeks
High VE in 1st year of life
Booster doses for tetanus needed to maintain circulating antibodies (though the number and intervals need to be defined)

3p+1 primary schedule plus infant booster (<1 year)
3 primary doses already ensure protection against DTP for the first year of life, so no infant booster required.

3p+1 primary schedule plus toddler boosting (1-6 years, preferably in 2nd year of life)
This schedule ensures protection for at least 6 years.

3p+1 primary schedule plus preschool booster
Greater reactogenicity of the booster dose than with aP; prefer aP for preschool booster

3p+1 primary schedule plus adolescent/adult booster
wP not licensed for the use in adolescents/ adults; aP should be used for adolescent / adult booster

Evidence to support/preventing the use of following DTaP schedule:

Age at first dose:
As early as possible ≥6 weeks.

3+0 primary schedule (none of the evidence has been assessed with a 6, 10, 14 weeks schedule)
High VE against pertussis in 1st year of life
Tend to be lower VE in 1st year of life than wP (although may not apply to all vaccines),) faster waning, lower boostability with increasing doses
Boosters doses for tetanus needed to maintain circulating antibodies (though the number and intervals to be defined)
No clinical evidence available (only seroresponses)

2p+0 primary schedule at 6, 10 weeks/ 6, 14 weeks
No evidence supporting either schedule without additional doses
Immunogenicity will most likely be insufficient
Concerns that this schedule would create a window of vulnerability for pertussis

2p+1 primary schedule at 6, 10 weeks plus infant booster
No evidence available to support this schedule (accelerated priming)
Immunogenicity will most likely not be sufficient
Concerns that this schedule would create a window of vulnerability for pertussis between the 2nd dose and the booster

2p+1 primary schedule at 6, 14 weeks and infant booster (9-12 months) :
No data from LMIC
Demonstrated efficacy of 2 doses of aP against hospitalisation/mortality (Scandinavian countries, Italy – though with later initiation of the schedule) but later protection is questionable
Risks of this schedule:
Tendency for lower VE than effective wP and faster waning.
Limited boostability with increasing doses?
Reduced coverage and delayed DTP3 coverage may lead to less protection in children having received only 1 dose for many months
Transient reduction of infant Ab responses in presence of maternal antibodies (significance?)

6-14 weeks and toddler booster (2nd year of life):
Waning efficacy after two doses of aP containing vaccine (P and D)

3p+1 primary schedule plus infant booster (<1 year)
No evidence available

3p+1 primary schedule plus toddler boosting (1-6 years, preferably in 2nd year of life) / preschool booster
Proven effective to prevent infant pertussis mortality
Booster dose should be based on the local epidemiology
Booster dose should be based on the aim of the immunization program

3p+1 primary schedule plus adolescent/adult booster
No evidence available

Evidence on timing of boosting (aP and wP):

Toddler booster (2nd year of life)
Useful after 3 primary doses of aP vaccine to reduce morbidity in young children and reduce exposure of infants (based on epidemiology)
Lower reactogenicity with aP than wP

Preschool booster (4-6 years)
Useful to reduce pertussis morbidity in school children (based on epidemiology)
The pre-school boosting is also beneficial for sustained protection against tetanus and diphtheria

Pertussis vaccine was considered to be the main driver of the deliberations on the use of different schedules, given its relative importance in particular in light of protecting infants against pertussis-related mortality. It was reemphasised that the recommended immunization schedules should ensure a maximum of flexibility to countries in order to tailor immunization schedules based on their local epidemiology, the objective of their immunization program as well as to programmatic issues. There are gaps in knowledge for the timing of diphtheria and tetanus boosters in order to rationalize the optimal schedules to achieve long term or lifelong protection

The working group underlined the recommendation that the first primary DTP dose should be given **as early as possible ⩾6 weeks of age**. Thus, later schedules (e.g. 3, 5, 11 months) were not further discussed.

In terms of the data on the different schedules, the working group concluded that there was no evidence in support of any 2p+0 primary schedule, 2p+1 primary schedule at 6-10 weeks plus infant booster, or 3p+1 primary schedule plus adolescent/adult booster.

Concerning a 2p+1 schedule at 6-14 weeks plus an infant booster (9-12 months), even given the high effectiveness of 2 doses of wP and aP against pertussis death, the main risk was assessed to be related to excess deaths if DTP2 dose was only given at 14 weeks (or later, in real life) as this would lead to an increased risk in children having received only 1 dose until the age that they are given DTP2. A primary series at 6, 10, 14 weeks would likely lead to a higher coverage of children with DTP2 at an earlier age.

On a 3p+0 primary schedule at 6, 10, 14 weeks, the high vaccine effectiveness against pertussis infant mortality was underlined. Protection against diphtheria seems to be sufficient with 3 primary doses in most settings. For tetanus, boosters would be needed to ensure circulating antibodies i.e. continuous protection.

A 3 primary doses plus toddler boosting (1-6 years, preferably in 2nd year of life) / preschool booster schedule demonstrated duration of protection and high vaccine effectiveness against pertussis for 6 years. Dependant on the aim of the immunization program and the local epidemiology, administration of a booster would a) reduce pertussis morbidity in children, b) reduce exposure of infant siblings to pertussis, c) ensure continued protection against tetanus and diphtheria beyond the first year of life.

Implication for Hib vaccine

Further the working group discussed the possible impact and implications for Hib vaccines particularly for countries using pentavalent vaccines. For Hib vaccines the two key factors are the need for an 8 weeks interval between dose 1 and dose 2 when a 2 primary doses plus a booster (2+1 schedule) is used; and if a 6,10,14 weeks schedule is used the uncertain need for a booster to ensure longer term protection. As stated in the *Haemophilus influenza* type b vaccination position paper – July 2013[18], there is currently insufficient information to determine whether or not there is a need for a booster dose, which may be influenced by local epidemiology, co-administered vaccines, and the potential for natural boosting as well as other factors.

Hence, when using a Hib containing pentavalent vaccine is used, this would advocate against a 6w, 10w, 9m 2p+1 schedule. The working group acknowledged that the 4th dose of hepatitis B within the pentavalent vaccine was administered essentially for programmatic issues, though it is assumed that administering the third dose later within this schedule would be rather beneficial.

A 3 primary doses plus toddler booster and d) when using a pentavalent vaccine, ensure continued protection against Hib beyond the first year of life

The working group concluded that concerning the timing of the pertussis booster dose, no revisiting of the current statement was needed, as it was clearly phrased and there was no new information regarding this schedule. The pertussis booster dose should be administered at 1-6 years preferably in 2nd year of life (booster 6 months after primary doses). This contact could further be used as catch-up for other vaccines. This schedule should ensure protection for at least 6 years for countries using wP vaccine. For countries using aP, protection may not last as long as evidenced in the USA and Australia.

In conclusion the WG recommended the following:

1. **That on the grounds of protection against pertussis, diphtheria and tetanus the current schedule remains the preferred option for countries where it is currently used as there is no compelling evidence to recommend a change to a 2+1 schedule (e.g . 6w, 10w, 9m or 6w, 14w, 9m).**

   This is because:

   Epidemiological evidence does not suggest that current wP and aP vaccines induce rapid waning within the first year of life which might favour a late dose at 9 months.

   Overall the epidemiological evidence indicates that there is additional benefit for pertussis from the 3rd dose and delaying its administration until 9 months may impact on course completion and, without rapid waning, would reduce overall protection against severe disease in the first year of life

   For pentavalent Hib-containing vaccines there is benefit for the Hib component from the 3rd priming dose if given with one month intervals between doses. If pentavalent DTPHepBHib vaccine is given as a 2+1 schedule then there needs to be 8 weeks between doses (i.e. this would require a 6w, 14w, 9m schedule). Delaying the second dose to 14 weeks of age would likely have deleterious effects on its coverage and on the protection against pertussis in the first year of life.

2. **That the pertussis booster dose should be administered at 1-6 years preferably in the 2nd year of life (booster 6 months after primary doses).**
   This contact could further be used a as catch-up for the administration of other vaccines.

3. **That countries which are currently successful using alternate primary vaccination schedules as witnessed by adequate surveillance, can continue doing so.**

4. **That before contemplating a move from a 3+0 to a 2+1 schedule, countries should seriously consider their current epidemiological situation, and the potential implications in terms of potential impact on pertussis and Hib in the context of the vaccination coverage achieved at different ages, as well as timeliness of immunization.**

5. **That given the costs inherent to any change, a change in vaccination schedule and strategy should be informed by data.**

6. **That it is important for countries to try to reach the highest coverage possible with the current vaccination strategy, and to implement disease surveillance.**

Whole Cell Pertussis Vaccines: Summary of evidence relevant to schedules

1a. Burden and epidemiology

- ✓ Pertussis is still a major public health problem
  - ❖ Approximately 16 million new cases occurred in the world in 2008, 95% in low and middle income countries
  - ❖ Estimated responsible for c. 195,000 (?) deaths in children annually; most deaths in infants and very young children
  - ❖ Case-fatality rate highest in very young infants
  - ❖ Prior to vaccination, nearly 80% children were infected with *Bordetella pertussis* by age 5 years, and an appreciable proportion (>50%) with clinical disease. Surveillance difficult and good data are sparse in the literature
  - ❖ **Since vaccines introduced, dramatic decline in number of cases.**

1b. Issues relevant to choice of schedule

Decisions on optimal vaccination schedules should take several factors into consideration:

- ✓ Age distribution of pertussis disease and pertussis attributable deaths in the population
- ✓ Implications of age at vaccine initiation, number of doses, interval between doses, waning of protection, reactogenicity, expected vaccine coverage and timeliness of vaccination for vaccine use, effectiveness and impact
- ✓ **Pertussis vaccine given as a combined vaccine, thus must consider implications for other antigens and target diseases**

1c. Vaccine immunogenicity

- ✓ Whole-cell pertussis vaccines (wP) induce a complex immune response to many bacterial antigens, including production of antibodies against *Bordetella pertussis* main virulence factors (PT, FHA, ACT, LPS, DNT, PRN, FIM2/3 and BrkA).
- ✓ No good serological correlate of protection identified
- ✓ **No good data comparing immunogenicity of three primary vaccination doses given in the first year of life in either 3p+0 or (2+1)p schedules**

1d. Vaccine effectiveness

- ✓ Consistent evidence from low and moderate quality studies (including 4 RCTs) that wP given in infancy as three primary doses at intervals of 4 to 8 weeks (3p schedules) protects against severe pertussis disease in the first 5 years of life.
- ✓ Consistent evidence, though from lower quality studies, that vaccination in infancy using (2+1) schedules (around age 3, 5 and 10-13 months) is effective in the first 5 years of life.
- ✓ No good data to compare schedules in term of effectiveness
- ✓ Limited evidence of incremental protection in the first 5 years of life with number of vaccine doses received.

Note: Heterogeneity between studies makes comparisons difficult:

- ❖ Different vaccine strains and case definitions
- ❖ Different duration of follow-up
- ❖ (2+1)p VE estimates do not include 1st year of life when disease most severe
- ❖ Limited data on effectiveness of 2p in infants under 12 months

1e. Current vaccines and safety data

- ✓ 64% countries currently use wP containing vaccines (including 96% in WHO AFR and 100% WHO SEAR);
- ✓ 86% of countries with wP vaccines use pentavalent DTwPHibHepB (91% in WHO AFR and 77% in WHO SEAR)
- ✓ Most common adverse reactions within 7 days of vaccination are fever (up to 59%), local swelling (up to 57%) and local pain (up to 65%).

1f. Current schedules, coverage and timeliness

- ✓ All wP countries give three doses in infancy, typically at 6-10-14 weeks or 2-4-6- months.

1g. Predicted impact of different schedules

- ✓ Depends on several assumption (see 1b above)
- ✓ Impact against mortality determined in particular by protection in early infancy, and thus vaccination at an early age
- ✓ Modelling suggests 6-10-14 week preferable to 6w-10w-9m schedule for reduction of pertussis deaths, except under assumptions of high effectiveness of second dose and rapid waning of vaccine-induced protection.

2. Whole-cell Pertussis Vaccines – detailed evidence

2a. Burden and epidemiology of pertussis

Pertussis (whooping cough) remains a major public health problem, especially in low and middle income countries (LMIC). The disease is caused by infection with *Bordetella pertussis*, a bacterium that is ubiquitous in human populations. The most severe manifestations of the disease include a protracted cough lasting several weeks, often accompanied by paroxysms that end with a characteristic inspiratory whoop. The disease can be fatal, especially in infants and younger children (Edwards 2013).

WHO estimates that there were approximately16 million cases of pertussis in the world in 2008, of which 95% occurred in developing countries, and that it was responsible for about 195,000 deaths. There is considerable uncertainty over these estimates.

Formalin-killed whole-cell pertussis vaccines (wP) were introduced widely in developed countries in the mid-20th century, and included in the Expanded Program for Immunization (EPI) in 1974. Their introduction has been credited with the steep decline in pertussis morbidity and mortality in children worldwide (Figures 1 and 2) Many high-income countries (HIC) introduced acellular pertussis vaccines (aP), containing 2 to 5 purified antigens, since 2000 (Von Konig 2009, Pertussis Vaccines-WHO Position Paper).

Whole-cell vaccines remain the most widely used pertussis vaccines in the world. In the majority of countries where they are employed, vaccination is given as a course of three primary doses administered at various intervals within the first year of life, followed in some countries by one or two boosters between 15 months and 5 years of age. Two schedules are most commonly used to deliver the primary immunisation course. In one, all three doses are given at approximately equal intervals of 4 to 8 weeks (referred to in this document as "3p", while in the other, two doses are given at short interval of about 2 months, with a longer interval (4-6 months) before the third dose (named "(2+1)p" in this document).

Fig 1. Pertussis reported global annual incidence and DTP coverage 1980-2013 (WHO pertussis Database 2015)
Note: only a small proportion (< 5 %) of actual cases are reported globally.

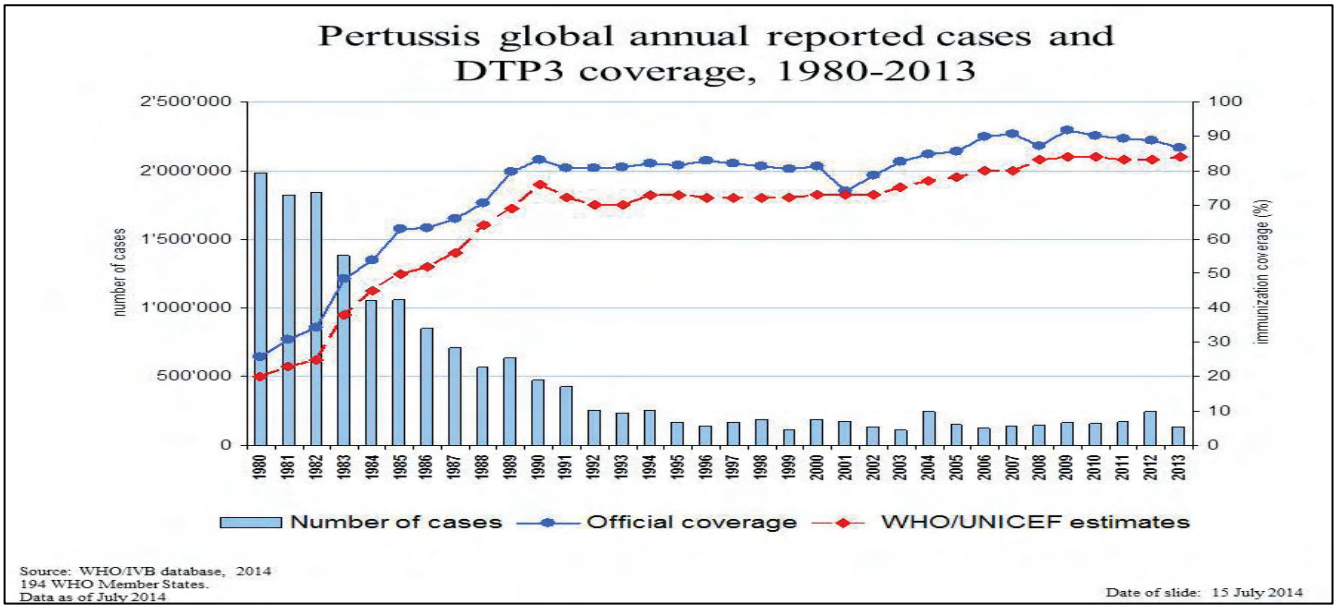
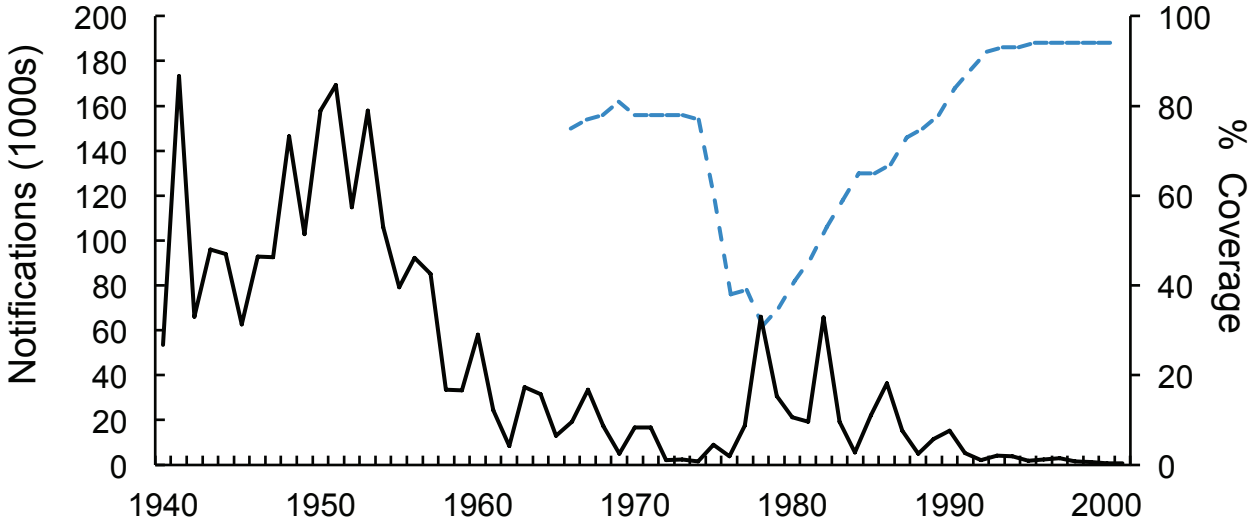


Figure 2. Notified pertussis incidence and whole cell vaccine coverage in England and Wales, 1940 – 2000. The vaccine was introduced in 1950s, and became national in 1957. Note cyclical epidemics and resurgence of



disease after decline in vaccine coverage in 1970s.

Pattern in pre-vaccination era

Limited data on the distribution of pertussis in unvaccinated (pre-vaccine) populations indicate that infection was ubiquitous, with most individuals infected in childhood, of whom an appreciable proportion, > 50 %, exhibited classical disease. Approximately 80% cases occurred in children under 5 years in some parts of the USA, and less than 3% cases in persons aged 15 years or above (Fales 1928). Case fatality rates were also high, in particular in infancy. Similar patterns were observed in other countries, including in Africa (e.g. Senegal, Kenya and South Africa) and South Asia (India). Examples of age distribution of pertussis disease and deaths in the pre-vaccination era are provided in figures 3 and 4.

Patterns in post-vaccination era

The introduction of effective infant vaccination with high coverage was accompanied by a steep decline in the number of pertussis cases and deaths in children worldwide. Pertussis surveillance remains difficult and in need of strengthening.

A shift toward pertussis in older age groups (adolescents and young adults) has been reported in recent years in some high income countries, in particular those which now use acellular pertussis vaccines. The age shifts may, in part, be explained by an increasing awareness and recognition of less typical disease manifestations in older subjects, as well as more sensitive laboratory testing. It has also been suggested that waning of vaccine-derived immunity, combined with lower naturally-acquired immunity and boosting (as a result of lower community transmission) may play a role in increased susceptibility in adolescents and adults.

Several high income countries which introduced aP vaccines experienced resurgence of pertussis in recent years, including relatively large numbers of cases in adolescents and adults. The reasons for these resurgences are not yet clear.

Fig 3: Pertussis notification rates, by age, in England and Wales pre (1953-56) and post (>1957) vaccination. Four year averages to cover epidemic cycles.

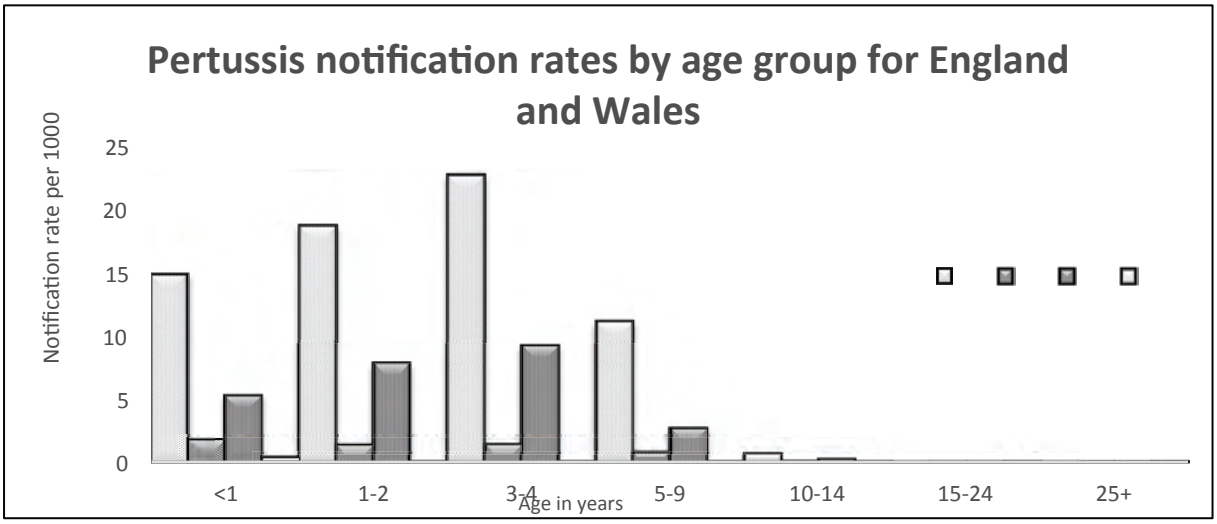
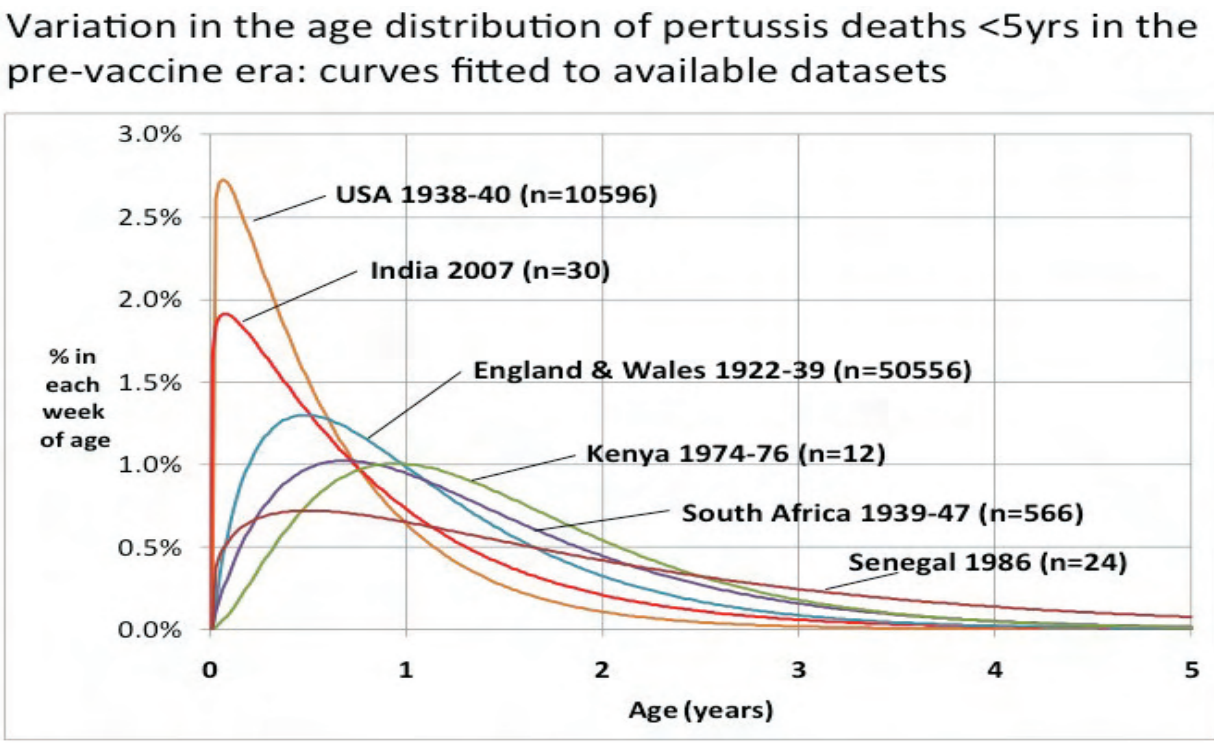


Figure 4: Examples of the age distributions of pertussis deaths reported in various settings in the pre-vaccine era *(Note that these are curves fitted to observed data (number of observations in each study in bracket), and represent relative frequencies. Details of observed data for each curve are presented in appendix 1. Note also the very small numbers of deaths in the studies in India, Kenya and Senegal, reported under conditions which may not be representative of the entire countries)*



2b. Issues relevant to choice of optimal pertussis vaccination schedule

Several factors need to be considered when choosing an optimal vaccine schedule, e.g.:

- Age distribution of pertussis disease and deaths
- Implications of age at vaccine initiation, number of doses and dose interval on VE
- Possible waning of vaccine derived (and natural) immunity especially in absence of boosting
- Reactogenicity and safety of the vaccine
- Expected vaccine coverage and timeliness of vaccination
- Vaccine-derived herd immunity
- Implications for other antigens and target diseases included in the combined vaccine
- There appears to be considerable heterogeneity between populations and between studies in disease patterns, and in vaccine effects, some of which is attributable to differences in case ascertainment and definition (see Appendix 2).

2c. Immunogenicity of primary course of vaccination

Immunogenicity data are difficult to interpret and compare for whole-cell Pertussis vaccines. There is no established immunological correlate of protection against pertussis disease (Von Konig 2009). Different wP vaccines may have different antigenic content, leading to variations in post-vaccination immune response. There are limited data in the literature, and much of the available information refers to vaccine formulations no longer in use. However, patterns of immune response may contribute insights on vaccine effectiveness.

Limited evidence from a systematic review (Mueller et al. 2014) suggests that the short-term immune response (few weeks to months post-vaccination) increases with the number of doses, and appears to be stronger with longer intervals between primary doses. Observational studies report higher antibody titres 6-8 weeks following the 3rd dose when given after ~ 6 months [i.e. (2+1)p schedule] than when given 1-2 months after the 2nd dose (i.e. 3p schedule).

Whole-cell pertussis vaccine induces a complex immune response to many bacterial antigens, including the production of antibodies against *B. pertussis* key virulence factors (PT, FHA, ACT, LPS, DNT, PRN, FIM2/3, BrkA). For details, see (Von Konig, 2009).

Despite the standardization of some aspects of the vaccine production process, considerable variation has been noted in the strain and quantity of bacterial material, and hence in the antigenic content of different wP vaccines. Consequently, it is difficult to directly compare the immunogenicity of different wP vaccines. Furthermore, the absence of any known correlate of protection implies that comparison of immunogenicity may not translate into differences in clinical effectiveness.

The assay used to assess whole-cell Pertussis vaccine lot potency for licensure remains the intracerebral mouse challenge test introduced in the 1940s, although it remains unclear what specific immune response is being assessed.

Immune response and age at initiation of vaccination

The evidence is limited. Wilkins et al (1987) reported an increasing trend in the proportion of children achieving a titre ≥1:80 when the 1st dose was given respectively at age 4-11, 12-19 and 20+ weeks. An RCT by Baraff et al (1984) found no evidence that a 1st dose at birth led to different immune response (anti-FHA IgG) after subsequent doses.

Immune response and number of doses

Using serum antibody titres a few weeks to months post-vaccination as the proxy-measure, there is limited but consistent evidence (Baraff 1984, Barkin 1985, Wilkins 1987) of increasing immune response with the number of doses received, compatible with a boosting effect of each additional dose.

Immune response and interval between of doses

The evidence suggests that a longer interval between doses is associated with a stronger immune response. In a US study (Wilkins 1987), a higher proportion of children with intervals between doses of 8 weeks or more achieved antibody titres ≥1:80 than did those with 3-7 week intervals, irrespective of age at vaccine initiation. A trial conducted by Barkin et al (1985) reported higher antibody titres 1-2 months after the 2nd dose given at a 4-month interval compared to 2 months.

Immune response and vaccination schedules

A systematic review found 4 observational studies with direct comparison of immunogenicity attributable to 3p and (2+1)p schedules within similar timeframe after vaccination, providing evidence of very low to low quality. Two studies (Olin 1998 & Booy 1992) contrasted immune response about 4 weeks after the 3rd dose, the third (Miller 1995) about 6 weeks after, and the fourth (Miller 1997) at 6 weeks and then at 12-18 months after the 3rd dose. All but one of the studies were based on the comparison of unrelated cohorts. Olin (1998) compared subjects randomised to the wP arm of a trial, but in which both schedules were used. There is some suggestion from Miller (1995) and Miller (1997), and marginally from Olin (1998) that post-vaccination anti-FHA and anti-PT are titres slightly higher 4-6weeks after the 3rd dose in children who received (2+1)p (3rd dose at ~11-13 m) compared to 3p (3rd dose at ~6m). This is consistent with the other studies that found apparent associations between intervals between doses and immune response.

There was no difference between schedules when antibody titres were compared at age 12-18 months, except for anti-FIM. Key results from these 4 studies are summarised in figure 5 below, showing the ratio and 95%CI of antibody Geometric Mean titres (GMTs) in (2p+1)/3p.

Type of evidence: Observational studies **Quality of evidence:** Very low to Low

Caution: Various limitations and potential for bias in different studies. Also, difficult to separate effect (on immune response) of interval between doses to that of age (e.g. 3p children receive 3rd dose at age 4-6 months whereas (2+1)p children do so at 11-13 months)

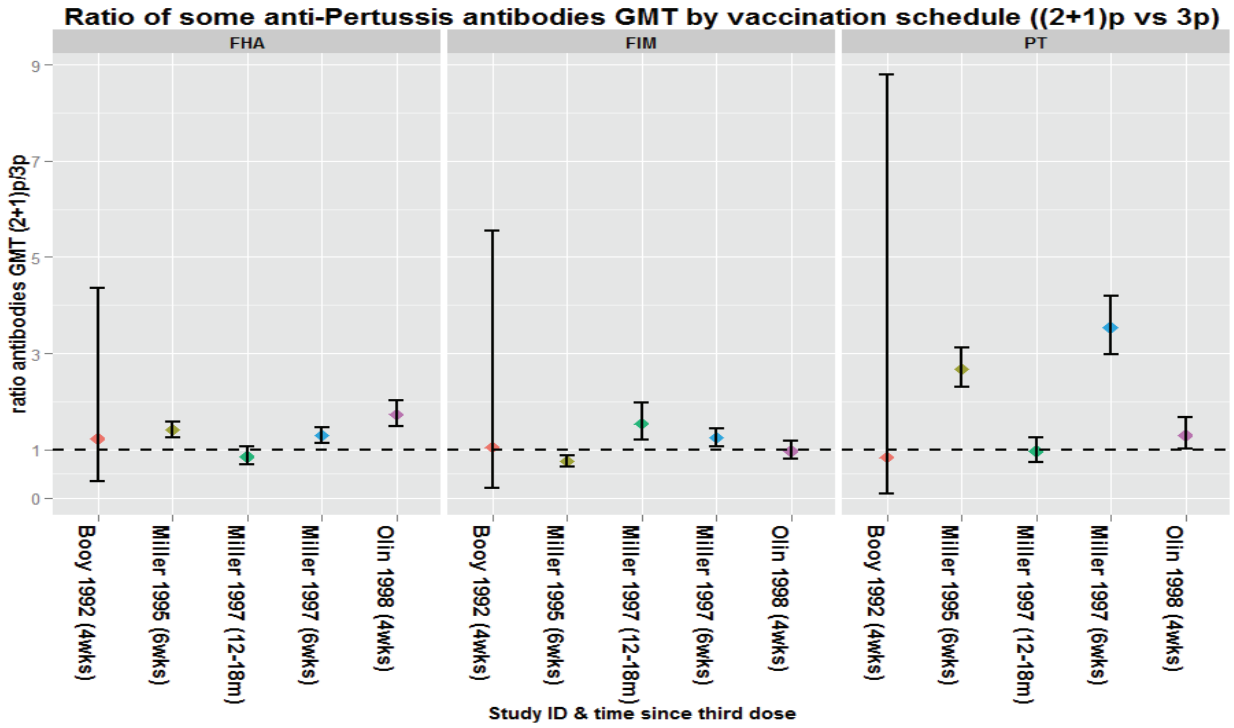


Fig 5. Comparison of three different anti-pertussis antibodies induced by (2+1)p versus 3p schedules, in terms of ratios of GMTs. ***Age or time since last dose given in parentheses****. (Note: ratio >1 means post-vaccination antibody Geometric Mean Titres (GMT) higher after (2+1)p compared to 3p)*

2d. Vaccine effectiveness against pertussis disease

The evidence summarised here (figure 6) is derived from an update to a systematic review (Mueller et al. 2014) of controlled trials, observational studies, and surveillance estimates using the screening method. Note that there are several complexities and sources of heterogeneity that may affect direct comparisons of estimates between studies, including:

(1) **Vaccine strain and batch used:** variability in vaccine strain, antigenic content, batch and immunogenicity. There are relatively few data on vaccine formulations currently in use.
(2) **Specificity of case definition:** This varies between studies from clinical diagnosis only to culture-confirmed cases only. A further complication is that the vaccines may protect best against severe disease (more typical and easier to diagnose clinically), with implications for VE measurement.
(3) **Differences in follow-up time:** Disease is most severe early in life, so dose timing and VE in infancy is very important. 3p schedules are typically completed between ages 4 to 6 months, whereas the 3rd dose in (2+1)p is given later at 11-13 moths.
(4) **Trends in vaccine-derived protection:** Evidence suggests VE may decline with time after vaccination, so it is necessary to compare schedules over similar follow-up times.
(5) **Context:** Most studies are relatively old, and the majority were conducted in high income countries where whole cell pertussis vaccines are no longer used. There are limited data from LMIC countries where community transmission rates may be higher with implications for age at infection, naturally-acquired immunity and boosting.

Note: Assessment and Ranking of Quality of evidence from the systematic review used the **GRADE approach (***GRADE working group, BMJ 2004***):**
High *= Further research unlikely to change confidence on estimates of effect;*
Moderate *= Further research likely to have an important impact on confidence in estimates of effect and may change estimates;*
Low *= Further research very likely to have an important impact of confidence in effect estimates and is likely to change estimates;*
Very low *= Any estimate of effect is very uncertain.*

Comparison of vaccine effectiveness by schedules

- ✓ **Very low to moderate quality evidence (including 4 controlled trials) that 3p schedules are effective against pertussis disease in the first 5 years of life.**
- ✓ **Very low to low evidence (no data from RCTs) that (2+1)p schedules are effective against pertussis at age 1-5 years (protection in under 1year old not included). Limited data on VE of 2 doses in infants under 1 years old.**
- ✓ **Very limited data on direct comparison of 3p and (2+1)p schedules; No direct evidence that either schedule is superior or inferior to the other.**

3p vs 0: ***Moderate evidence that 3p schedules are effective against pertussis disease***

Four trials measured the efficacy of wP given in 3 primary doses at 4-8 weeks intervals. Two trials [MRC (UK) 1951 and Blennow (Sweden) 1988] using the UK-Wellcome and the Sauer strains respectively found high VE up to 20-27 months after the 3rd dose (respectively 80% [95%CI 74-84] and 71% [95%CI 37-86]). Two later trials [Gustafsson (Sweden) 1996 and Giuliano (Italy) 1998] reported lower VE (48% [95%CI 37-57] and 31% [95%CI 9-45]). These later trials used a particular Connaught vaccine, and it has been suggested that the lower efficacy may have been due to the vaccine strain or to poor quality vaccine batches.

Evidence from observational studies is mostly consistent with the two older trial estimates and further suggest good protection in children up to age 5 years.

Type of evidence: RCTs and observational studies
Quality of evidence: Very low (3 screening and 3 case-control studies) to moderate (4 controlled trials)

(2+1)p vs 0: Low grade evidence that (2+1)p schedules are effective against pertussis.

There is no published controlled trial measuring the effectiveness of (2+1)p schedules. The available data come from 6 UK-based observational studies with moderate to high risk of bias. All studies except the two old household-cohort* studies found high effectiveness (ranging from 72% to 90%) of the (2+1)p schedule up to 4-5 years of age. VE estimates were lower in household cohort studies, respectively 24% [95%CI 11-35] (PHLS 1969 & 1973) and 53% [95%CI 45-60] (PHLS 1982). Note that VE estimates of completed (2+1)p by definition does not include protection in 1st year of life, given the 3rd dose is given at 11-13 months. The evidence on VE of 2 doses in children aged under 12 months is limited.

Type of evidence: Observational studies; **Quality of evidence:** Very low to low

Caution:

(1) Two of the four studies with relatively high VE are estimates using the screening method. This approach is highly dependent on assumptions regarding population vaccine coverage, has limited control for confounding by age and secular trends, and is vulnerable to other biases.

(2) *'Old' household-cohort studies used retrospective ascertainment of cases among household contacts of confirmed cases, which could lead to lower specificity of case detection and underestimation of VE. Also note that poor quality batches suspected as a contributing factor to lower wP VE in the UK in 1960s.

3p vs (2+1)p: ***Limited evidence to conclude whether schedule 3p or schedule (2+1)p has greater effect on risk of disease***

There are no controlled trial data that provide direct comparison of 3p against (2+1)p schedules. Olin et al (1998) contrasted VE of 3 doses at 2-4-6 months to 3-5-12 months for participants in a Swedish pertussis vaccines trial who were randomised to the wP arm. They found that this 3p schedule was marginally more effective (11% relative VE) than the (2+1)p schedule, but the difference was not significant (95%CI -89% to 57%). Limitations to the study include:

- follow-up was not comparable as the (2+1)p follow-up started much later than 3p, after age 1year; and
- The study was underpowered to evaluate this hypothesis, which was not its primary objective.

More generally, the direct evidence supporting effectiveness of 3p schedules appears stronger (2 trials) than that of (2+1)p schedules. However, in settings where both schedules were used and VE measured using similar methods (e.g. UK estimates using screening method and case-control study) and with similar case definitions, the effectiveness of 3p and (2+1)p appear comparable.

Vaccine effectiveness against pertussis-attributable death

The literature search did not identify any study that measured wP effectiveness against pertussis deaths. However, a review of the evidence by the WHO SAGE committee looked at severe pertussis morbidity and hospitalisation in infants less than 1 year of age. Given that the disease is likely to be more severe or fatal in infants, vaccine-induced protection against severe disease may apply to pertussis death. The review concluded that there was consistent evidence that a single dose of vaccine in infancy provided around 50% protection against severe disease, hospitalisation and death (ref SAGE background doc March 2014).

Effect on vaccine effectiveness of interval between 1st and 2nd dose

- ✓ **No within-study data available. Limited evidence from between-study comparisons that VE is no different with 3p at monthly or 2-monthly intervals**
- ✓ **No data on interval other than 2-monthly between 1st and 2nd doses for (2+1)p**

3p schedules:

Studies with data on effectiveness of 3p typically used 4-8 weeks intervals between primary doses. There was no study directly comparing the effect of different intervals on effectiveness.

A total of seven studies used 4-weekly doses, including 2 RCTS (MRC 1951 & Blennow 1988), one

cohort (Laurell 1957), 2 household cohort (Brink 1982 & Schmitt 1996), and 2 screening (White 1996 & Campbell 2012) studies.

Nine studies used 6 to 8 weeks intervals, including two RCTs (Gustafsson 1996 & Giuliano 1998), 1 cohort (Stehr 1998), 2 household cohort (Onorato 1992) & Simondon 1997), 3 case-control (Izurieta 1996, Liese 1997 & Bisgard 2005) and 1 screening (Guris 1997) studies.

Between-study comparisons do not suggest that the vaccine effectiveness systematically differs between schedules with 4-week intervals versus 6-8 weeks intervals between doses.

(2+1)p schedule:

All studies measuring effectiveness of (2+1)p schedules used the same interval (about 2 months) between the 1st and 2nd dose.

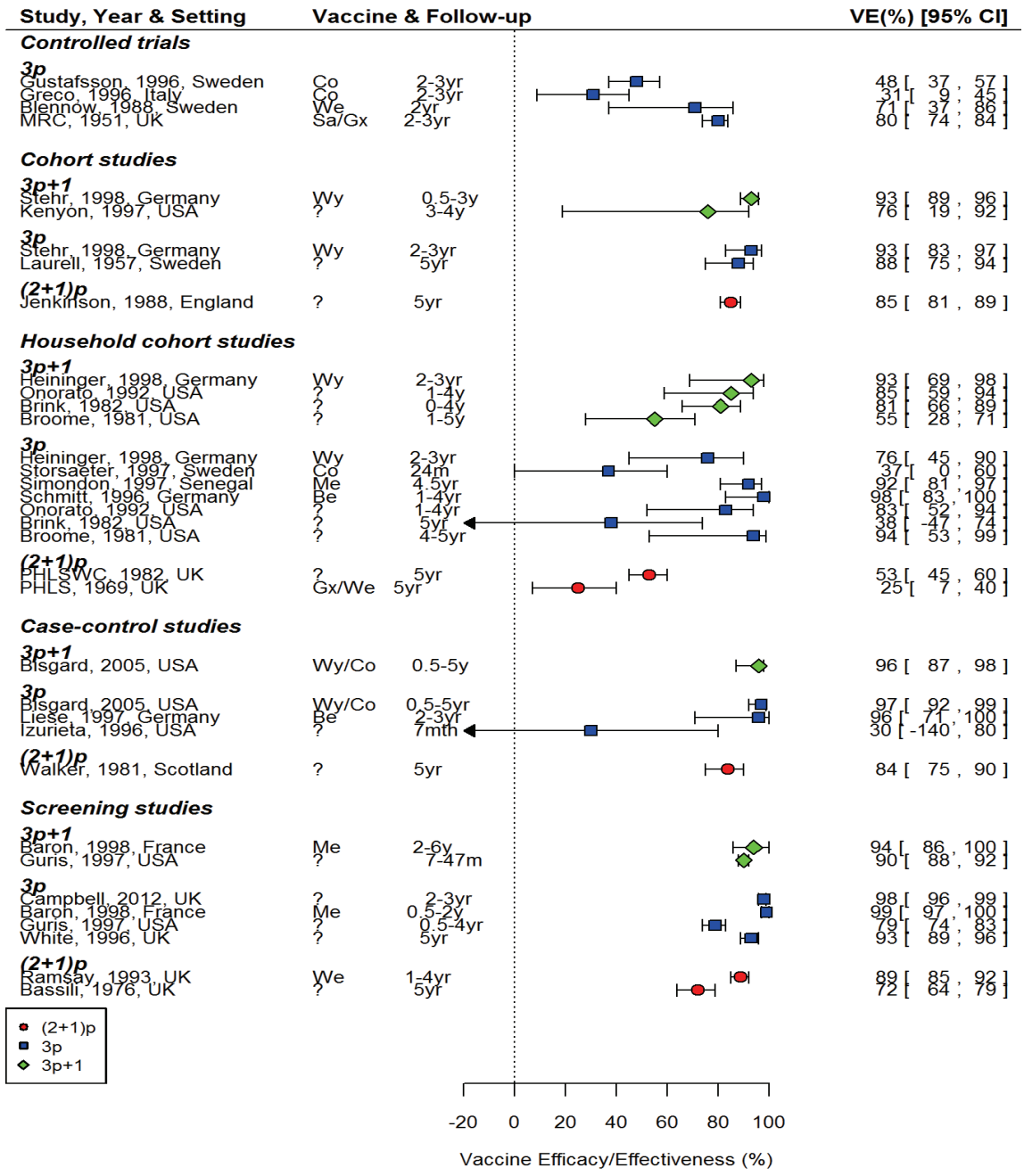


Figure 6: Summary of published data on whole-cell vaccine effectiveness against clinical pertussis

*(**Note: Vaccine abbreviations**: Be=Behring Co = Connaught, Gx=Glaxo, Me = Pasteur-Merieux, Sa=Sauer, We = Burrough-Wellcome, Wy=Wyeth-Lederle, ? = not mentioned in paper)*

Note (figure 6): *For studies reporting estimates using more than one* ***case definition****, the one included in the figure was chosen using the following hierarchy [Culture confirmed > New WHO/CDC confirmed > Old WHO > Clinical + culture/serology > Clinical + Epi-link > Clinical Only] in order to present the most specific (See appendix 2 for most commonly used case definitions).*

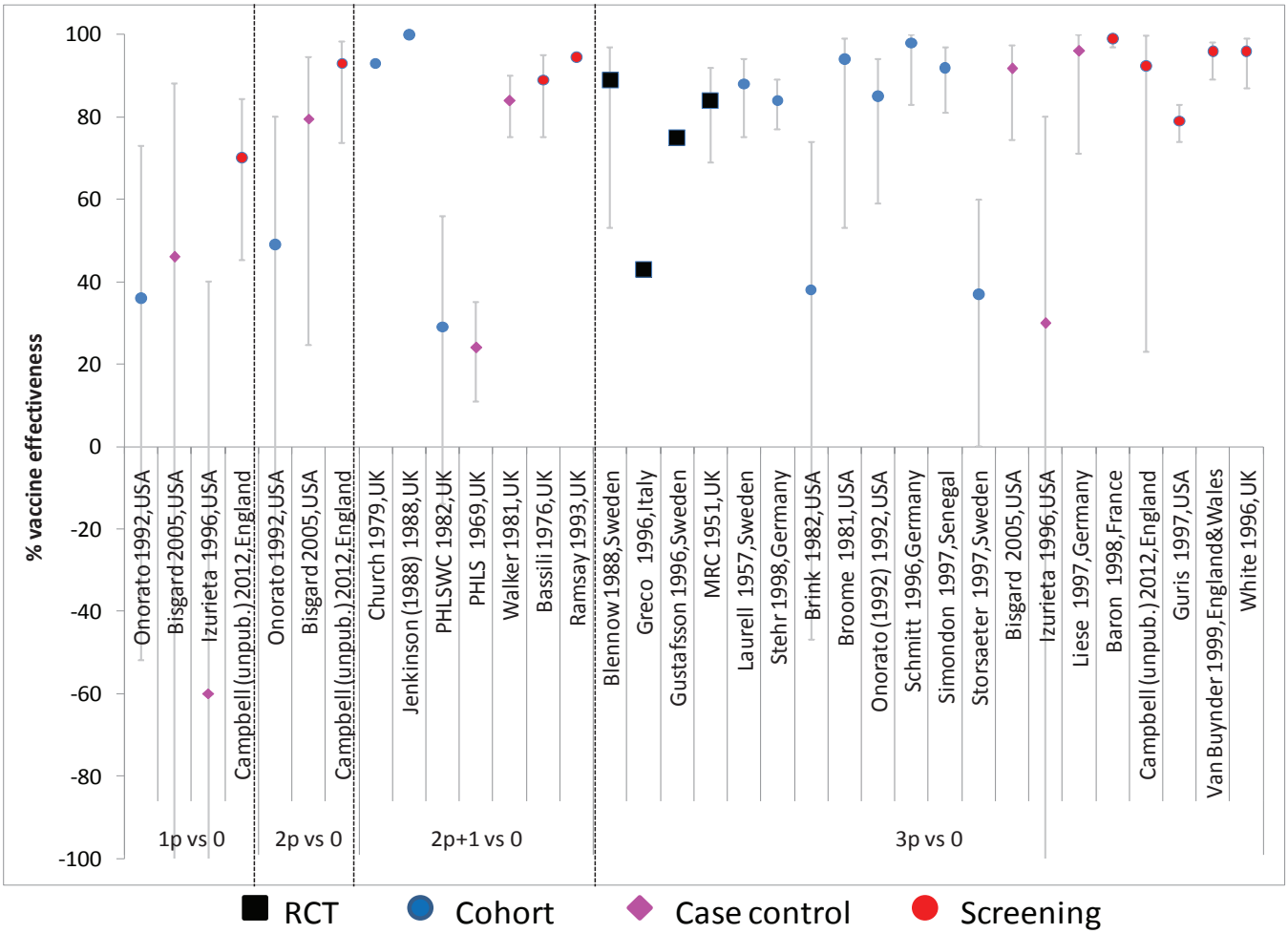
Age at initiation of first dose and vaccine effectiveness
✓ **Data on effectiveness are only available for schedules initiated around 2-3 months, not earlier.** ✓ **There is no within study comparison of VE of similar regimens starting at 2 months versus later age. Between-study comparisons provide no evidence on whether wP vaccine efficacy is different when the 1st dose is given at 2 or 3 months.** ✓ **There is low grade evidence (1 small RCT) that antibody response to a primary vaccination course is similar whether or not an additional dose is given at birth.**
In all studies measuring wP VE, the vaccination schedules were initiated at around 2 to 3 months of age, except the MRC trial (1951) in which the 1st dose was given between 6 and 18 months. **3p schedules:** All but 2 studies initiated vaccination in infants at around 2 months old, and there is low to moderate Grade evidence (from 3 trials, 2 cohort, 3 household cohort, 3 case-control and 3 screening studies) of vaccine protection after 3 doses, with VE estimates of up to 80% (95%CI 58-90) in one RCT (Blennow 1988). One household cohort study (Schmitt 1996) evaluated a 3p schedule with initiation at 3 months, and estimated VE at 97.6% (95%CI 83-99.7) up to age 2 years. The other study (MRC RCT, 1951) in which vaccination was initiated between 6-18 months of age found VE = 80% (95%CI 74-84) after ~27 months follow-up. **(2+1)p schedules:** All studies using (2+1)p schedules were carried out the UK where vaccination was initiated in infants around age 3 months.
Type of evidence: RCTs and observational studies **Quality of evidence:** low to moderate

Childhood boosters
✓ **3p: Very low grade evidence on effect of booster dose in children under 5 years. Limited evidence of benefit.** ✓ **(2+1)p: No evidence relating to additional effectiveness of booster dose in children under 5 years**
3p schedules [3p+1 vs 3p+0]: No RCT directly compared primary vaccination with and without booster in children under 5 years. Three studies (2 household cohort [Brink 1982 & Heininger 1998] and 1 screening [Guris 1997]) reported higher VE in children <5 years who had been given a booster. Three other studies (1 cohort [Stehr 1998], 1 household cohort [Onorato 1992] and 1 case-control [Bisgard 2005]) measured similar VE in children with and without booster. **(2+1)p schedules [(2+1)p+0 vs (2+1)p+1]:** A single (2+1)p study (PHLS 1969 household cohort) reported on the effect of a childhood booster. The interval between the last dose and booster dose was not reported, and there was no evidence of better protection in children <5 years who received the booster compared to those with complete (2+1)p vaccination (31% [95%CI 0-72%] higher attack rate in group with booster compared to those with no booster).
Type of evidence: Observational studies **Quality of evidence:** Low to very low **Caution:** (1) It is not clear from most studies if complexities linked to follow-up were considered, notably whether follow-up and estimates were restricted in both groups (with and without booster) to the period after booster was given. (2) Most observational studies were not designed to measure effect of booster doses, so likely underpowered.

Number of doses and vaccine effectiveness
✓ There is some low quality evidence from one cohort (Onorato), one case-control (Bisgard et al. 2005) and one Screening study (Campbell et al. unpublished) that a single dose is associated with some clinical protection against pertussis. ✓ The evidence (e.g. Walker 1981, Broome 1981, Onorato 1992, Bisgard 2005, Campbell 2014 Unpublished) is consistent with incremental protection with increasing number of doses received up to the 3rd dose, although the data are weak. ✓ The evidence on effectiveness by number of doses is summarised in figure 7.

Figure 7: Dose specific Vaccine Effectiveness of whole cell pertussis vaccines against pertussis disease

(NB: using VE estimates for shortest and earliest reported follow-up since last dose in order to approximate maximum vaccine-induced protection immediately after the dose).



Vaccine effectiveness and duration of protection

Duration/Waning of protection (figure 8)

- ✓ There is limited evidence on how wP VE changes with time since vaccination in children up to 10-16 years old. However, the data are consistent with decline of VE in time.
- ✓ Duration of immunity acquired after wP vaccination is estimated to range from 4-12yrs
- ✓ The actual rate of decline in VE remains unclear, as well as the explanation. It could be due to waning in vaccine-derived protection, or by progressive acquisition of natural immunity by the unvaccinated population, or both.
- ✓ The reasons for the decline have implications for estimation of vaccine impact.

3p schedules:

Six observational studies (MRC 1965, Blennow 1988, White 1996, Gustafsson 1996, Van Buyden 1999, Campbell 2012) with some data on VE by time since vaccination suggest progressive decline over time, starting as soon as 1-2 years after the 3rd dose. The most dramatic decline is reported in data from Gustafsson (1996) with a drop of VE from ~75% 0-6 months after the 3rd dose to ~34% after 18-24 months follow-up. However the decline in VE appears more modest in other studies, and only three report VE beyond 60 months (5 years).

(2+1)p schedules:

Five observational studies (Bassili 1976, Church 1979, PHLS 1982, Jenkinson 1988, Ramsay 1993) consistently suggest decline in VE starting between 1-2 years after third dose. For example Jenkinson (1988) report a decline from around 90-100% in 1-2 years old to about 50% VE in 5-6 years old. But the decline is less dramatic in other studies.

Caution:

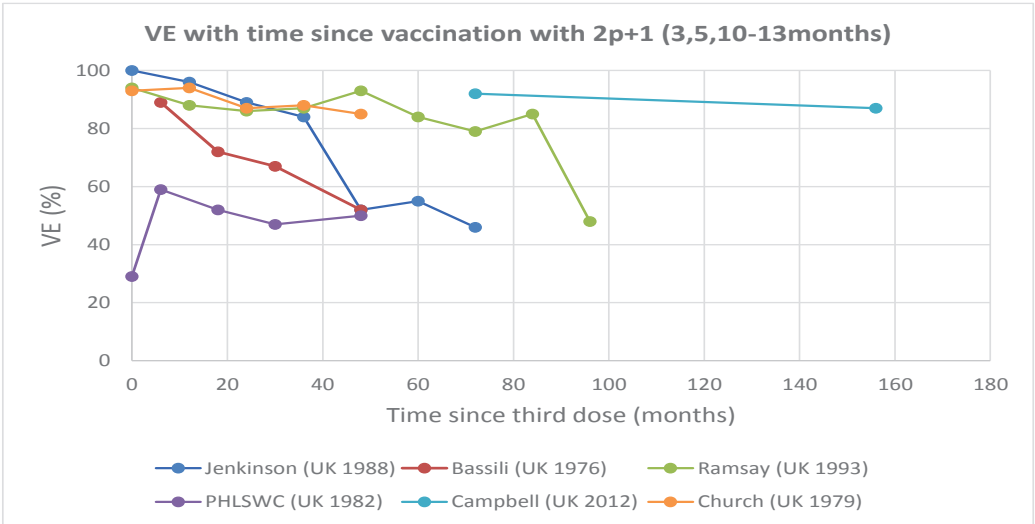
Although the overall pattern is consistent, the evidence is weak; studies contributing data are of very low to low quality, with several limitations and high risk of bias. Interpretation is unclear (see above).

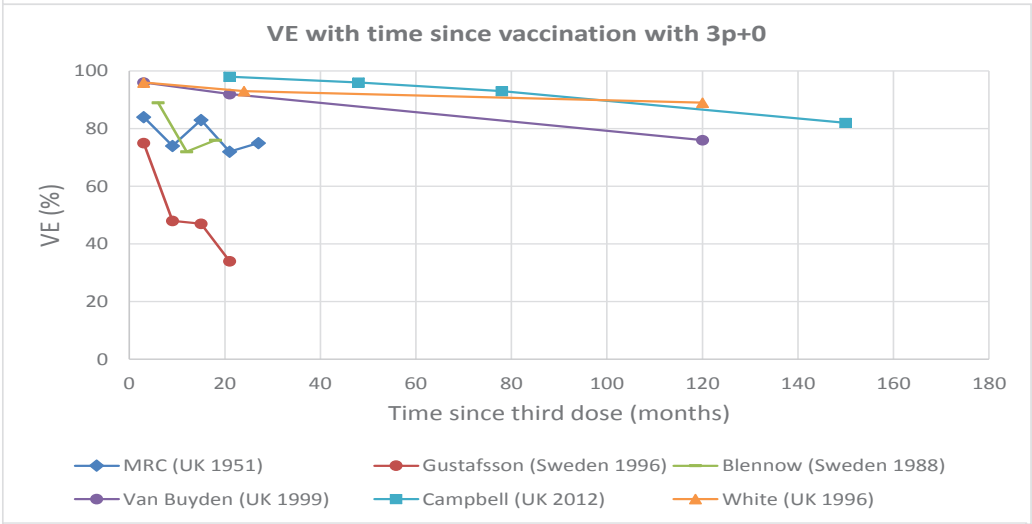
Effect of booster vaccination in children older than 5 years and adolescents:

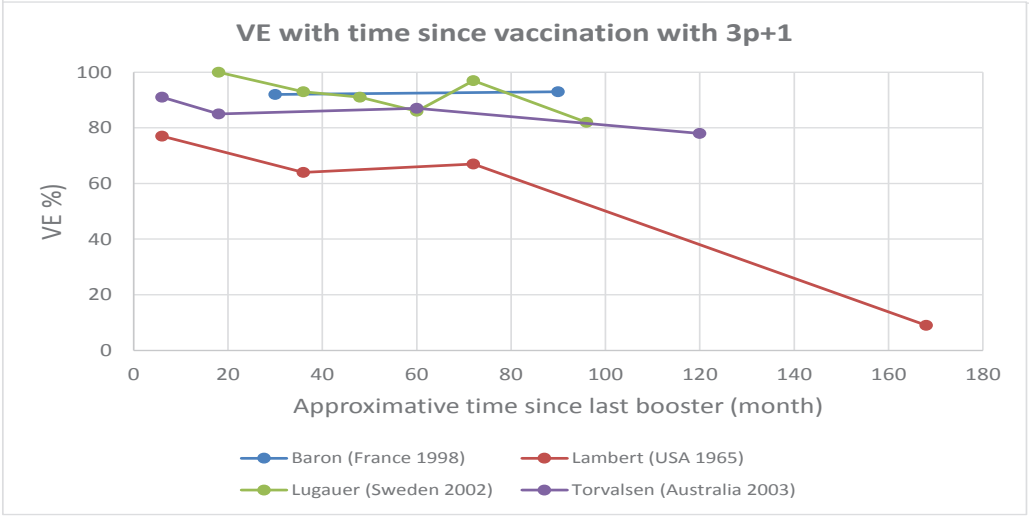
There are no data on the effectiveness of booster vaccination (using whole-cell or acellular pertussis vaccine) in children aged over 5 years.

Until recently, pertussis disease in adolescents and adults was not considered an important problem, and the risk of adverse reactions precluded any routine use of a booster wP in older children (Van Konig 2009). As a result there are very few data on the efficacy of booster vaccination in children over 5 years and adolescents.

Figure 8: Data on apparent decline in observed effectiveness of pertussis vaccines with time since last dose, after three different schedules: (2+1)p; 3p+0; or 3p+1.







2e. Reactogenicity and safety of whole-cell pertussis vaccines

- ✓ **Whole-cell pertussis vaccines are associated with systemic (e.g. fever, vomiting) and local (e.g. swelling, redness, pain/tenderness) adverse reactions in the days following vaccination.**
- ✓ **There is limited evidence that the risk of adverse events after the third vaccine dose is higher in children using the (2+1)p schedule than those using a 3p schedule.**
- ✓ **There may be considerable differences between vaccines in this respect.**

Overview of evidence on absolute reactogenicity of whole-cell pertussis vaccines

The reactogenicity and safety profile of whole-cell pertussis vaccines has been summarised in several reviews (Von Konig, 2009). There is good evidence that wP vaccines are associated with a relatively high rate of systemic (fever, vomiting) and local reactions (swellings, redness, warmth, pain/tenderness etc.). Comparisons of multi-component vaccines with and without wP (e.g. DTwP vs DT) suggest that wP is the most reactogenic component and responsible for the majority of immediate post-vaccination adverse reactions.

Three trials using the 3p schedule (Gustaffson 1996, Greco 1996 & Long 1990) reported high incidence of systemic (up to 7 to 12 times more fever), and local reaction (including local tenderness, redness and/or swelling) as soon as 24-48 hours after each dose of DTwP, compared to DT only. Findings from observational studies were consistent with these results.

The association of wP vaccines with less common post-vaccination reactions (hypotonic hypo-responsive episodes and seizures) is less certain. The trial by Greco et al (1996) found no significant difference in the rate of these two adverse events up to 48 hours following the administration of any dose of either DTwP or DT in infants.

Vaccination schedules and reactogenicity

Two cohort studies (Ramsay 1992 & Miller 1997) compared the reactogenicity of wP given in 3p monthly versus (2+1)p (3, 5 and 9-11 months) schedules, with data presented for each vaccination dose in the study by Ramsay (1992). The risk of fever, local redness and swelling seemed to increase after the third dose in the (2+1)p schedule, compared to the 3p schedule in which the frequency of adverse reactions appears similar after all three doses. Children vaccinated using the 3p schedule had 56% less fever, 50% less redness and 40% less local swelling after the third dose than children vaccinated in the (2+1)p schedule.

An RCT (Wong 2008) compared 3p schedules at 4 weeks (3,4,5 months) and 6-8 weeks (1.5,3,5months) intervals respectively, and reported broadly similar risks of adverse reactions.

Method: Systematic review **Type of evidence:** RCTs and observational studies **Quality of evidence:** Low to moderate
Caution: No trial or purposely designed study available to compare reactogenicity of 3p and (2+1)p schedules

2.f. Currently used wP vaccines and safety data from manufacturers

- ✓ **Sixty-four (64%) countries currently use wP containing vaccines, including 45/47 (96%) in WHO AFR region and all 13 countries in WHO SEAR region (see Figure 9).**
- ✓ **Pentavalent DTwPHibHepB is the most widely used wP containing vaccine (~86% countries using wP vaccines), with respectively 43/47 (91%) countries in WHO AFR and 10/13 (77%) countries in WHO SEAR regions.**
- ✓ **The Serum Institute of India's DTwPHibHepB (Pentavac) is used in over 50% countries using pentavalent wP vaccines, including two-thirds of WHO AFR countries.**
- ✓ **Evidence suggests that whole-cell pertussis is the most reactogenic component of wP containing vaccines, thus responsible for most of the adverse reactions.**
- ✓ **The most common adverse reactions within 7 days of vaccination include fever (up to 59%), local swelling (up to 57%) and local pain (up to 65%).**
- ✓ **Acellular pertussis (aP) vaccines are less reactogenic than whole-cell.**

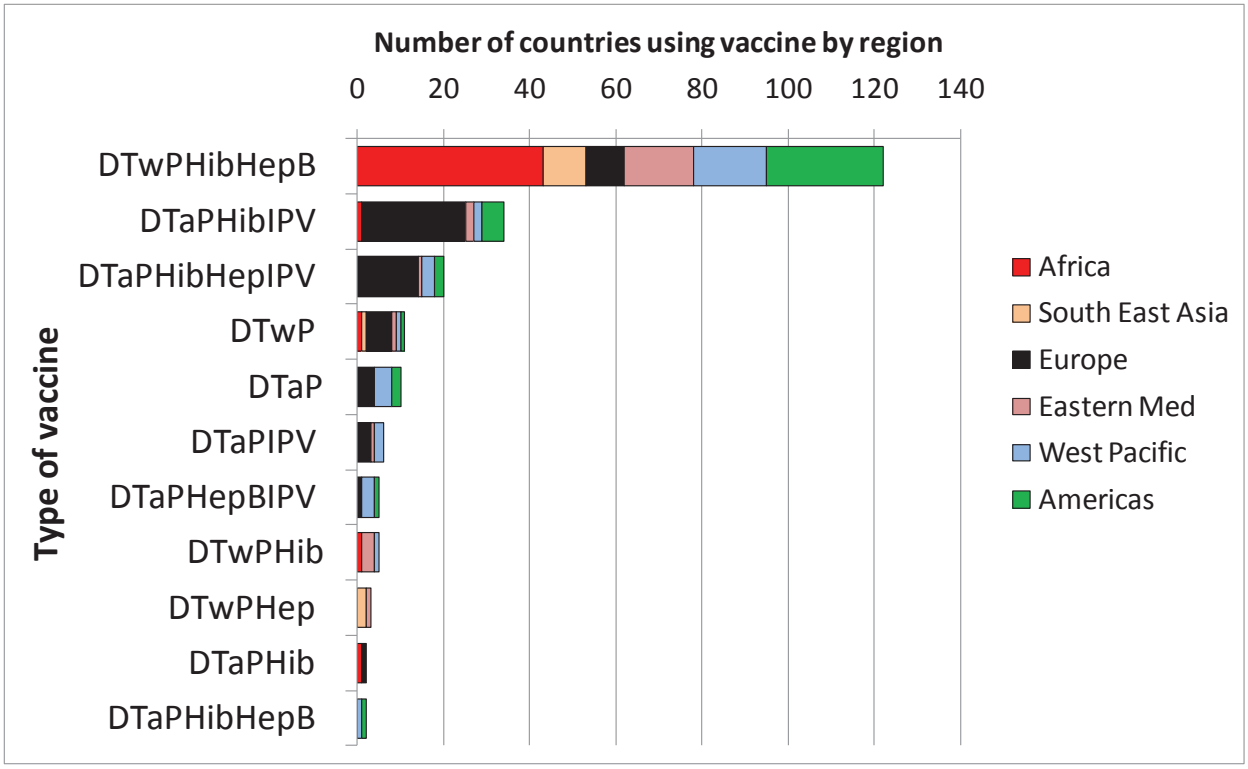
Currently used wP containing vaccines

Across the world, 142/223 (64%) countries currently use wP containing vaccines, with 122/142 (86%) of them using pentavalent DTwPHibHepB vaccines*.
Nearly half of countries using wP containing pentavalent vaccines employ the Serum Institute of India brand (Pentavac), including two-thirds (29/43) of countries in the WHO AFR region.

A	B	C	D
WHO region (N)	**# (% of A) Using wP containing vaccines**	**# (% of A) Using pentavalent DTwPHibHepB**	**# (% of C) Using SII Pentavac**
AFR (n=47)	45 (96%)	43 (91%)	29 (67%)
AMR (n=39)	28 (72%)	27 (69%)	8 (30%)
EMR (n=26)	21 (81%)	16 (62%)	5 (31%)
EUR (n=64)	15 (23%)	9 (14%)	2 (22%)
SEAR (n=13)	13 (100%)	10 (77%)	5 (50%)
WPR (n=34)	19 (56%)	17 (50%)	7 (41%)

**Note: some countries use more than one schedule/vaccine (e.g. for specific sub-groups)*

Fig 9.Number of countries using each type of DTP combination, grouped by region



Manufacturer safety data

The most commonly reported post-vaccination adverse effects are systemic (fever, drowsiness, and vomiting) and local (pain, redness, and swelling). Local reactions within 7 days after vaccination appear to be more common with wP containing than acellular vaccines, and the rates seem to decrease with subsequent vaccination doses.
Fever is frequently reported in the 7 days following vaccination with either aP (range between studies = 29-59%) or wP (range between studies = 12-48%) containing vaccines, although the incidence of grade 3 or more severe fever is higher after wP (up to 27%).
Studies also reported between 4-65% local pain (with up to 24% grade 3 or more severe) after receipt of wP containing vaccines, and 2-57% local swelling (with up to 49% grade 3 or more severe). The reported rate of most common adverse reactions after SII's Pentavac, the most

widely used pentavalent wP containing vaccine, are given in the table below.

Adverse reaction rate (%) up to 7 days after DTwPHibHepB from SII (Pentavac) vaccination* (grade 3 or more severe)			
	1st dose (6 weeks)	**2nd dose (10 weeks)**	**3rd dose (14 weeks)**
Fever	41.2 (17.5)	41.2 (17.5)	28.6 (13)
Vomiting	3.7	2.4	1.6
Drowsiness	2.3	0.2	0.4
Swelling	41.2 (39.1)	36.3 (35.1)	29.8 (28.9)
Pain	57.6 (22.4)	51.8 (21.6)	41.6 (15.5)
Redness	21.2 (19.6)	17.1 (15.5)	14.7 (13)

*Data from Phase III multicentre RCT in India(Sharma 2011)

2g. Current schedules, coverage and timeliness

The table below summarises typical pertussis vaccine schedules currently in use. For further details, see Appendix 5. Note that most high income countries currently use acellular pertussis containing vaccines, while the majority of LMICs use whole cell pertussis containing vaccines.

Income level	WHO region	DTP visits						Typical vaccine
		1p	2p	3p	Boost ~1yr	Boost ~5yrs	Boost ~15yrs	
Low / Middle	Africa South East Asia Western Pacific	6w	10w	14w	-	-	-	DT**wP**HibHepB
	Eastern Europe	2m	3m	4m	18m	-	-	
	Eastern Mediterranean Latin America	2m	4m	6m	18m	~5yrs	-	
High	North America Western Europe Western Pacific	2m	4m	6m	12m -18m	~5yrs	15yrs (few)	DT**aP**HibIPV

All except 3 countries using wP containing vaccines currently administer primary vaccination using a 3p schedule. In most countries in WHO AFR (39/43), WPR (11/16) and SEAR (5/9) primary pertussis vaccination is given at 6,10 and 14 weeks, whereas the majority in AMR (24/26) and EMR (12/18) administer the vaccine at 2,4 and 6 months. In WHO EUR, 7/14 wP countries give primary vaccination at 2, 3 and 4 months

Three countries report using a long interval between the 2nd and 3rd dose, including Jamaica (6,10 weeks and 9 months), Tunisia (2,3 and 6 months) and Poland (4,8 weeks and 7 months). At least one childhood booster dose is administered (between age 15 and 24 months) in 69/127 (54%) countries using wP vaccines [respectively AFR (6) AMR (24) EMR (15) EUR (14) SEAR (5) WPR (5)].

Coverage and timeliness of wP containing vaccines vary considerably between countries. Figure 10 shows coverage and timeliness of primary DTP vaccination doses in Kenya, Senegal and India from DHS survey data, and in England from Public Health England data. Grey/blue lines in the Kenya, Senegal and India figures refer to measles vaccine, which achieved coverage greater than DTP3 but less than DTP2 in the second year of life in each of these countries.

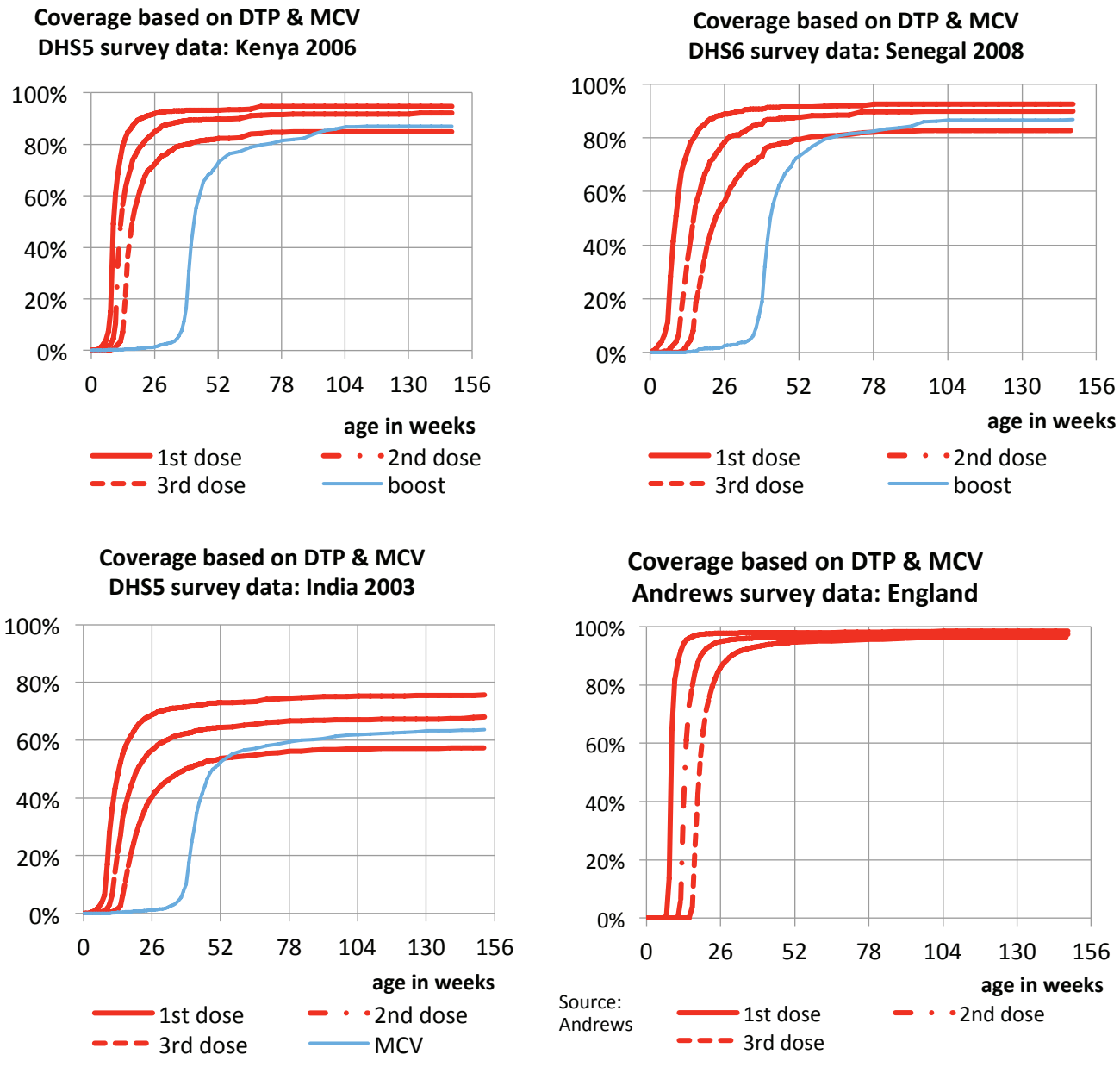


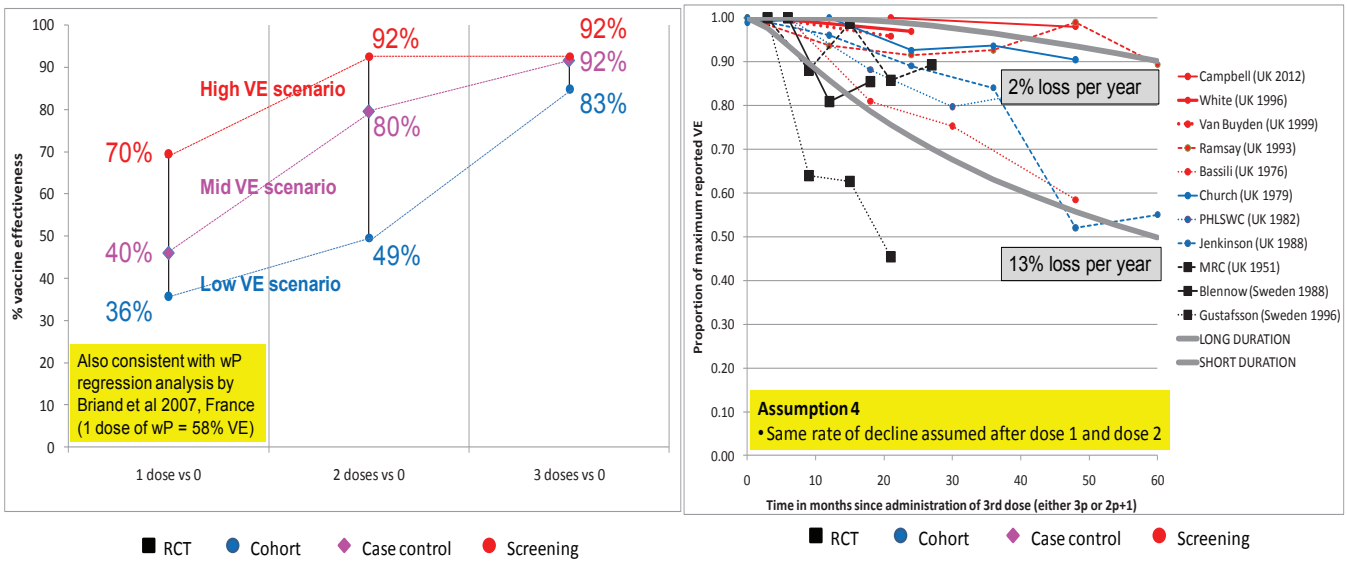
Figure 10. Examples of coverage and timeliness of DTP vaccination in three LMIC (Senegal, Kenya and India) and one high income (England) countries.

2h. Potential impact of different schedules

Impact prediction requires several assumptions, in particular on the background pattern of disease and on vaccine effectiveness by number of doses received, as well as on any decline in VE-induced protection with time since vaccination. Figure 11a shows an example of a set of assumptions on effectiveness by dose, based upon data in Figure 7. Figure 11b shows an example of a set of assumptions on waning protection, based upon data in Figure 8.

Figure 11. Scenarios of vaccine protection after each dose of wP using studies that report on all 3 doses (11a) *(with VE expressed as the highest reported VE for studies with multiple follow-up points)* **and relative clinical protection by time since the 3rd dose of wP (11b)**

(a) Vaccine protection after each wP dose* (b) Relative clinical protection**



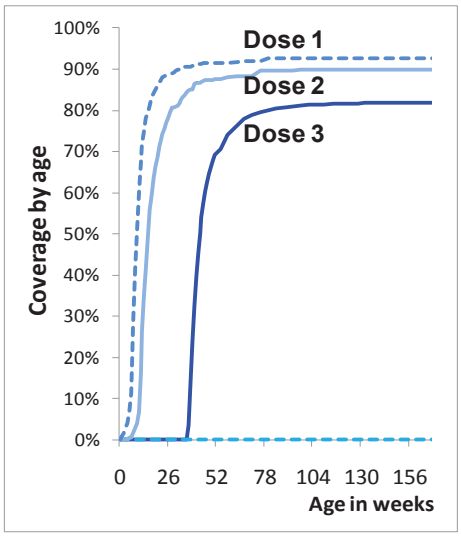
** Note (11a). Studies were restricted to those reporting on all three doses. The relationship between the VE reported for each dose within the same study was maintained in each scenario. The high VE scenario is based on unpublished screening data from a wP cohort aged 9w-6m in England (see Campbell 2012). The mid scenario is based on children aged 6-23m in a case control study in the USA (Bisgard 2005) and the low scenario is based on children aged 1-4yrs in a cohort study in the USA (Onoratu 1992). It is assumed there would be a 2 week period before vaccine protection starts and waning vaccine-induced protection begins.*

*** Note (11b). For example, if a study reported 90% VE after 3m and 45% after 60m, this would be expressed as 1.0 at 3m and 0.5 at 60m.*

Model results are shown in Figures 12 and 13. Figure 12 shows how the impact on deaths due to pertussis of whole cell pertussis vaccination, at 6w-10w-9m is estimated. The baseline age distribution of deaths from pre-vaccination era – see Figure 4 and appendix 1 – is in red. Coverage and timeliness from DHS data for Senegal, 2008 (Figure 10) are used to estimate the proportions of deaths "covered" by successive doses, represented by blue shading (b). The proportions of deaths prevented are based on vaccine effectiveness of 36%, 49% and 83% (for doses 1, 2 and 3 respectively) with 2% waning per year after administration of each dose.

Figure 12. Example of modelled coverage (a), coverage of pertussis deaths (b) and direct impact* against pertussis deaths (c) of wP vaccination (6w-10w-9m) in Senegal.

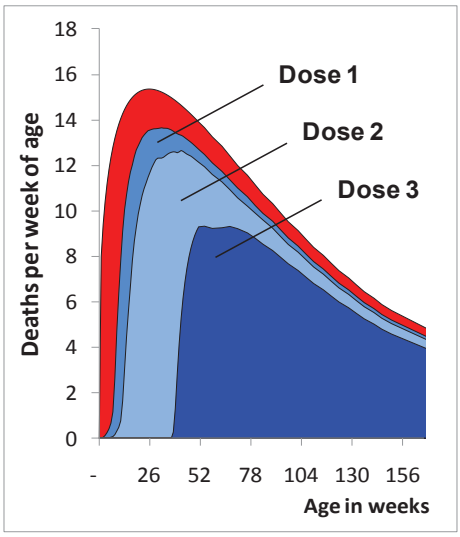
(a) Coverage by age



Timeliness by age and dose:
DHS 2008

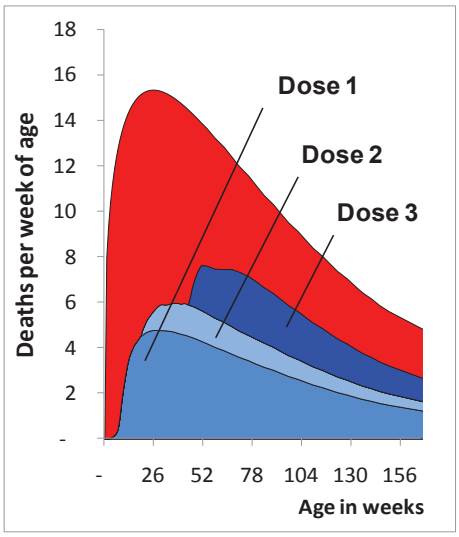
Current coverage by dose:
WUENIC 2011

(b) Coverage of deaths by age



Age distribution of deaths:
Preziosi et al, *Am J Epi 2002*

(c) Direct effectiveness by age



Protection after each dose (wP):
Mueller/Djomo review, 2015

Duration of clinical protection (wP):
Mueller/Djomo review, 2015

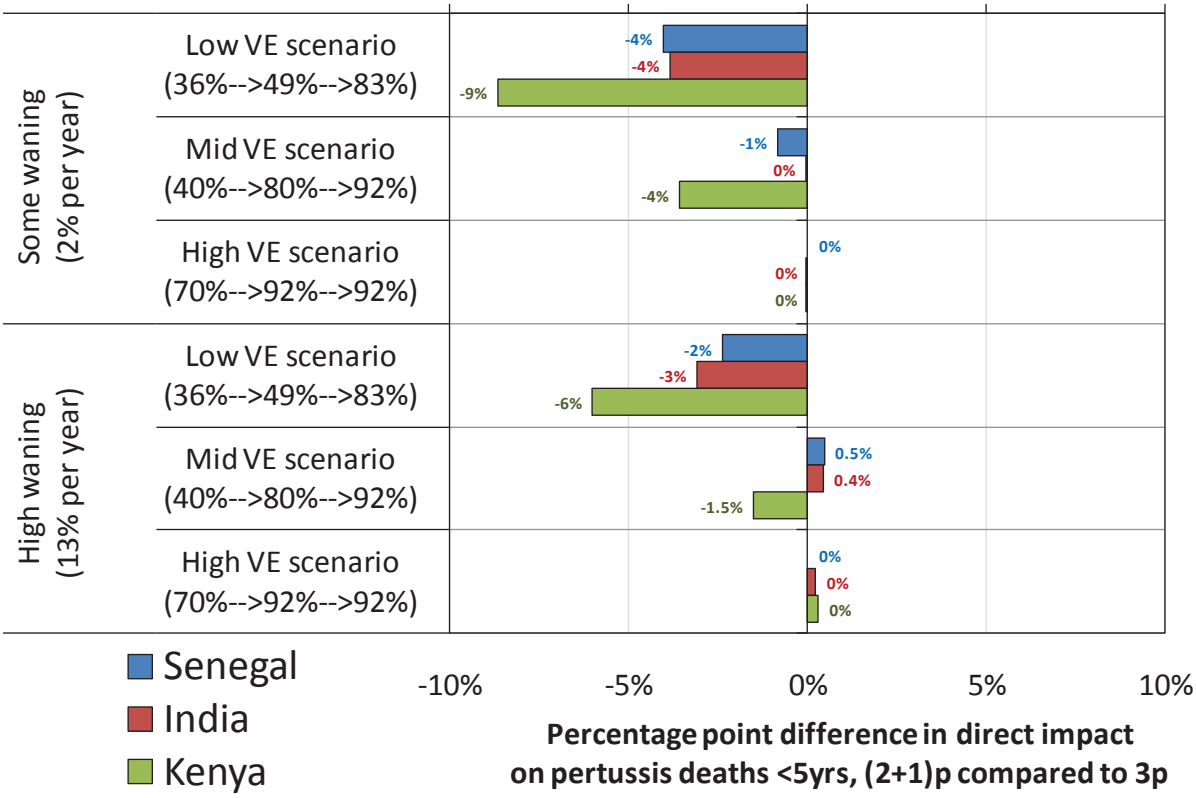
**Note (12c). The blue shaded areas on chart 12c represent the number of pertussis deaths that could be prevented by each dose, accounting for the dose-specific coverage, effectiveness and duration of vaccine-induced protection among wP vaccine recipients, excluding herd immunity considerations.*

Figure 13 shows the percentage point difference in direct impact of 6w-10w-9m schedule compared to the current 6-10-14w schedule used in India, Kenya and Senegal under different assumptions relating to effectiveness by dose (see Figure 7), age distribution of deaths (see Figure 4) and magnitude of waning per year (see Figures 8 and 11b). The direct impact of the 3p schedule is subtracted from the direct impact of the (2+1)p schedule to estimate the absolute difference in direct impact. Thus, positive differences indicate better direct impact with the (2+1)p schedule. Negative differences indicate better direct impact with the current 3p schedule. A major determining factor of the difference is the assumed protection level immediately after the second dose, here illustrated as 49 % versus 80% and 92 %.

A low VE scenario with limited waning would favour the existing 6-10-14w (3p) schedule in all countries. A 6w-10w-9m ([2+1]p) schedule is slightly favoured if the second dose VE is high (>80%) and protection wanes rapidly (13% per year). There are subtle differences between the three countries, which reflects differences in the age distribution of deaths (earlier in India see figure 4 and appendix 1) and differences in the coverage of each dose (higher and more timely in Kenya and Senegal – see figure 10), highlighting the need to account for local circumstances where possible.

Other variations (e.g. in age distribution of deaths and timeliness) were explored in further models using Senegal as an example (see appendix 4).

Figure 13. Percentage point difference* in direct impact against pertussis deaths in children <5yrs: (2+1)p [6w-10—9m] compared to 3p [6-10-14w] in Senegal, India and Kenya



**Note (fig 13). The direct impact of the 3p schedule is subtracted from the direct impact of the (2+1)p schedule to estimate the absolute (percentage point) difference in direct impact. Thus, positive differences indicate better direct impact with a (2+1)p schedule. Negative differences indicate better direct impact with the current 3p schedule*

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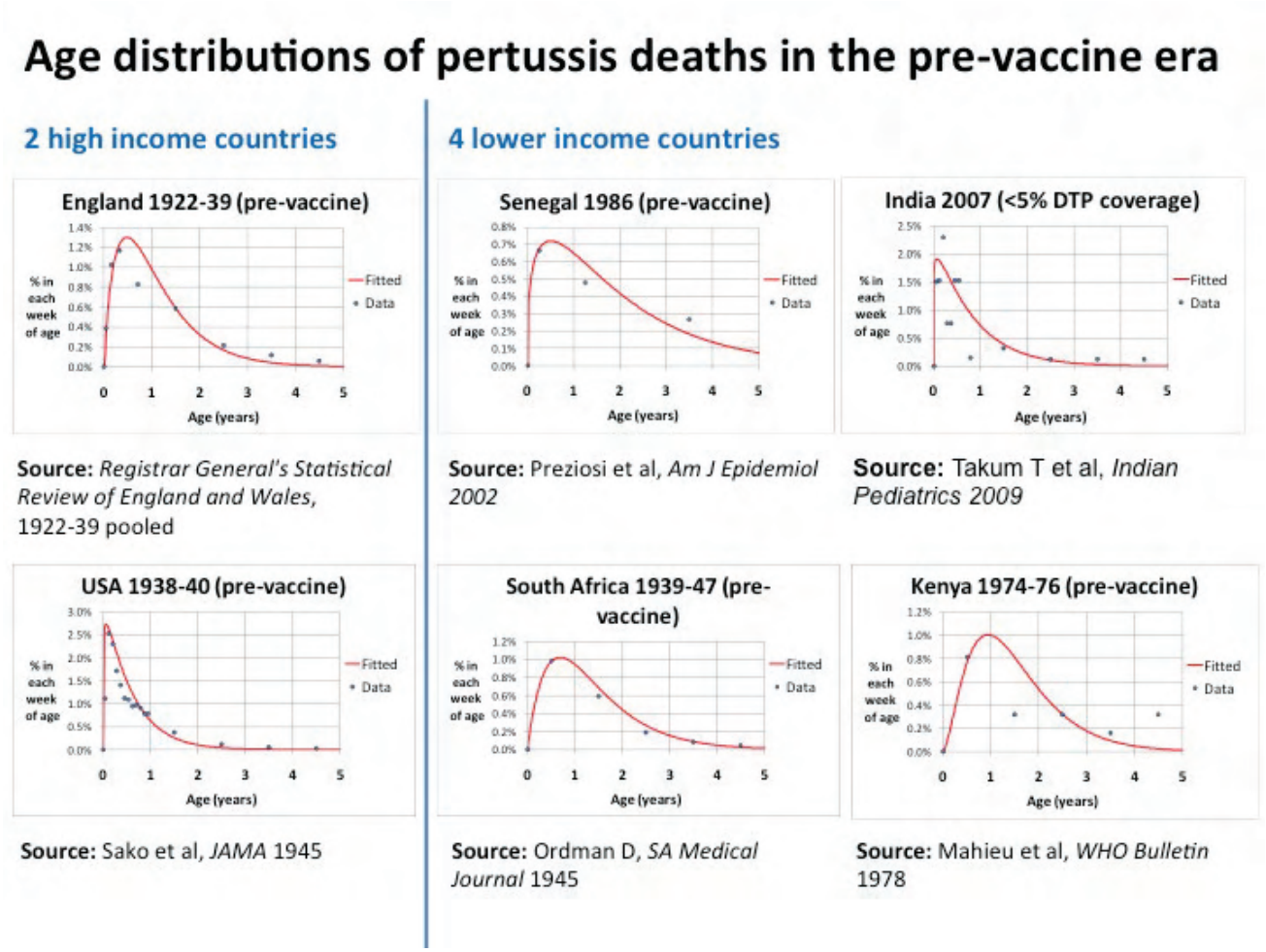
Appendix 1: Example of observed age-distribution of pertussis deaths in pre-vaccine era



Appendix 2: Some commonly used case definitions in wP vaccine efficacy studies

Case definition	Clinical		Culture	PCR	Serology	Epi-link
WHO Old	>21 days	AND ANY OF	Yes	No	Yes	Yes
WHO New	>14 days	AND ANY OF	Yes	Yes	Yes	Yes
CDC Clinical	>14 days	AND ANY OF	No	No	No	No
CDC Confirmed 1 (CDCC1)	>14 day	AND ANY OF	No	Yes	No	Yes
CDC Confirmed 2 (CDCC2)	>1 day	AND ANY OF	Yes	No	No	No
Laboratory confirmed (LC)	Varied	AND ANY OF	Yes	Yes	Yes	No

**Clinical* include cough + characteristic signs depending on study (paroxysm, inspiratory whooping, post-tussive vomiting)

Appendix 3: Details of studies with estimates of Vaccine Effectiveness

Schedule	Study	Year	Setting	Strain	Design	Timing	Age gp	F/up	VE (%) by Case definition (95% CI)					
									Clin ± lab	Clin only	Culture	Old WHO	New WHO	CDC Conf
(2+1)p														
(2+1)p	Jenkinson	1988	UK		2.Coh	3-5m (+11/13)	1-5yrs		85 (81-89)					
(2+1)p	PHLS	1969	UK	Gx/We	4.Cca	3-5m (+10)	0-4yrs		25 (7-40)					
(2+1)p	Walker	1981	UK		4.Cco	3-5m (+10)	6m-5yr		84 (75-90)					
(2+1)p	PHLSWC	1982	UK	Gx/We	3.Cca	3-5m (+10)	1-4 yr		53 (45-60)					
(2+1)p	Bassili	1976	UK		5.Scr	3-5m (+10)	1-5yrs		72 (64-79)					
(2+1)p	Ramsay	1993	UK	We	5.Scr	3-5m (+10)	1-4 yr			89 to 94				
(2+1)p	Campbell	2012	UK		5.Scr	3-5m (+11)	5-9yr				92 (49-98)			
(2+1)p	Campbell	2012	UK		5.Scr	3-5m (+11)	10-16yr				87 (69-95)			
3p														
3p	MRC	1951	UK	Sa/We	1.RCT	3 monthly		~27m	78 (74-82)		80 (74-84)			
3p	Blennow	1988	Sweden	We	1.RCT	2-3-4m	6-23m	~20m	80 (58-90)	93 (70-98)	71 (37-86)			
3p	Greco	1996	Italy	Co	1.RCT	2-4-6m	6-23m	~17m		27 (5-43)	43	36 (14-52)	31 (9-45)	
3p	Gustafsson	1997	Sweden	Co	1.RCT	2-4-6m		~18m			41 (30-51)	48 (37-57)		
3p	Laurell	1957	Sweden		2.Coh	2-3-4m	< 5 yr		88 (75-94)					
3p	Stehr	1998	Germany	Wy	2.Coh	2-3.5-5m	0.5-3yr		78 (62-88)		84 (77-89)	93 (83-97)		
3p	Broome	1981	USA		3.CCa	2-3-4m	1-4yr		94 (53-99)					
3p	Brink	1982	USA		3.CCa	2-3-4m	0-4yr		38 (-47-74)					
3p	Onorato	1992	USA		3.CCa	2-4-6m	1-4 yr						83 (52-94)	
3p	Schmitt	1996	Germany	Be	3.CCa	3-4-5m	0.5-5yr					98(83-100)		
3p	Simondon	1997	Senegal	Me	3.CCa	2-4-6m	1-4yr		74 (55-85)			92 (81-97)		
3p	Storsaeter	1997	Sweden	Co	3.CCa	2-4-6m		~24m				29 (2-48)		
3p	Storsaeter	1997	Sweden	Co	3.CCa	2-4-6m		~24m				37 (0-60)		
3p	Heininger	1998	Germany		3.CCa	2-3.5-5m	4-5yr		76 (45-90)					
3p	Izurieta	1996	USA		4.CCo	2-4-6m	<7m							30 (-140 to 80)
3p	Liese	1997	Germany	Be	4.CCo	2-4-6m	<2yr		95 (81-99)			96 (71-100)		

3p	Campbell	2012	UK		5.Scr	2-3-4m	40-59m				96 (92-98)			
3p	Campbell	2012	UK		5.Scr	2-3-4m	5-9yr				93 (89-95)			
3p	Campbell	2012	UK		5.Scr	2-3-4m	10-16yr				82 (41-93)			
(2+1)p + Booster														
(2+1)p+1	PHLS	1969	UK	Gx/We	4.CCo	3-5m (+10)(+/-B)	0-4yrs		24 (11-35)					
(2+1)p+1	PHLS	1969	UK	Gx/We	4.CCo	3-5m (+10)(+/-B)	5-10 yrs		25 (-10 to 49)					
3p + Childhood Booster														
3p+1	Kenyon	1997	USA		2.Coh	2-3-4m (+12/18)	19-47m							76 (29-92)
3p+1	Stehr	1998	Germany	Wy	2.Coh	2-3.5-5m (+15/18)	0.5-3yr		85 (78-90)			93 (89-96)		
3p+1	Broome	1981	USA		3.CCa	2-3-4m (+12/18)	1-5a		55 (28-71)					
3p+1	Brink	1982	USA		3.CCa	2-3-4m (+12/18)	0.5-4yr		81 (66-89)					
3p+1	Onorato	1992	USA		3.CCa	2-3-4m (+12/18)	1-4 yr		78 (44-91)				85 (59-94)	85 (59-94)
3p+1	Heininger	1998	Germany		3.CCa	2-3.5-5m (+15/18)	4-5yr		91 (66-98)			93 (69-98)		
3p+1	Bisgard	2005	USA	Co/Wy	4.CCo	2-4-6m (+12/18)	0.5-5yr		97 (92-99)					96 (87-98)
3p+1	Guris	1997	USA		5.Scr	2-3-4m (+12/18)	7-47m		92 (90-93)					90 (88-92)
3p+1	Baron	1998	France	Me	5.Scr	2-3-4m (+16-18)	2-6yr		92 (81-100)			94 (86-100)		
3p+1	Baron	1998	France	Me	5.Scr	2-3-4m (+16/18)	6-12yr		93 (85-100)			94 (87-100)		

***Vaccine strains abbreviations**: Be=Behring Co = Connaught, Gx=Glaxo, Me = Pasteur-Merieux, Sa=Sauer, We = Burrough-Wellcome, Wy=Wyeth-Lederle*

***Study design:** 1.RCT = Controlled trial; 2.Coh = Cohort; 3.Cca = Case-contact (household); 4.Cco = Case-control; 5.Scr = Screening Method*

Case definition: CDC Conf = CDC confirmed case; Clin only = Clinical only; Clin ± lab = combination of Clinical and laboratory other than WHO/CDC classic

Appendix 4: Further details on the models and additional scenarios

Methods

Whole-cell pertussis (wP) vaccines are used, and will continue to be used (WHO WER July 2014), in most low and middle income countries (LMICs) where the greatest pertussis disease burden exists. A modelling approach previously used to inform optimal schedules for Hib vaccination (WHO WER April 2013) was used to infer simple estimates of the benefits of alternative wP vaccination schedules in selected LMICs, namely India, Kenya and Senegal. The 3p (6-10-14w) schedule currently used in all three countries was compared to two alternative (2+1)p schedules, 6w-10w-9m and 6w-14w-9m. The 9m option was evaluated because all three countries currently administer the first dose of measles vaccine at this age, and data are available on the coverage and timeliness of this visit. The modeled outcome was the direct impact of wP vaccination, defined as the predicted percent reduction in all pertussis deaths <5 years, accounting for the coverage, effectiveness and duration of vaccine-induced protection among wP vaccine recipients. Pertussis deaths were the modelled outcome of interest since mortality reduction is the main priority for pertussis vaccination schedules in LMICs. Herd immunity considerations were not included in these estimates because the available data from these settings are of insufficient quality to accurately capture the age-specific incidence of infection, duration of natural protection, wP vaccine effectiveness vs natural infection, social contact patterns etc.

Best-fitting age distributions of pertussis deaths <5yrs were used to estimate the proportion of pertussis deaths occurring in each week of age <5yrs, assuming no deaths could occur in the first week of life (van Hoek AJ et al, Euro Surveillance 2013). Pre-vaccine era age distributions were based on 30 deaths in India (Takum T et al, Indian Pediatrics 2009), 24 deaths in Senegal (Preziosi et al, Am J Epidemiol 2002) and 12 deaths in Kenya (Mahieu et al, WHO Bulletin 1978).

Estimates of the coverage and timeliness of the first three doses of DTP (scheduled at 6, 10 and 14 weeks) and the first dose of measles vaccine (scheduled at 9 months) were based on dates reported on vaccination cards in large household surveys (India DHS 2005; Kenya DHS 2008; Senegal DHS 2010)(Figure 12a). In each week of age, the number of deaths potentially covered by each dose was calculated (Figure 12b). This was converted into direct impact (Figure 12c) by assuming different scenarios of vaccine protection after each dose (assumed to start 2 weeks after dose administration) and different scenarios of waning clinical protection after each dose (Figure 11). The estimates used in these scenarios were based on wP studies identified in reviews by Mueller (2014) and Nguipdop-Djomo et al. (2015). The effectiveness of each dose against pertussis cases was assumed to be a conservative proxy for effectiveness against pertussis death.

Additional Scenarios

Several additional scenarios were also evaluated (Figure below):

(i) Firstly, given the small numbers involved in fitting the age distributions in India, Kenya and Senegal, a conservative scenario was run based on the pre-vaccine era age distribution in the USA (Sako et al, JAMA 1945). This was the most heavily skewed distribution to

younger ages of all the pre-vaccine era distributions identified in the review (Figure 4). In this scenario, labeled '6w-10w-9m (age shifted left)' there was limited advantage of the 6w-10w-9m schedule, even under assumptions of high VE and rapid waning;

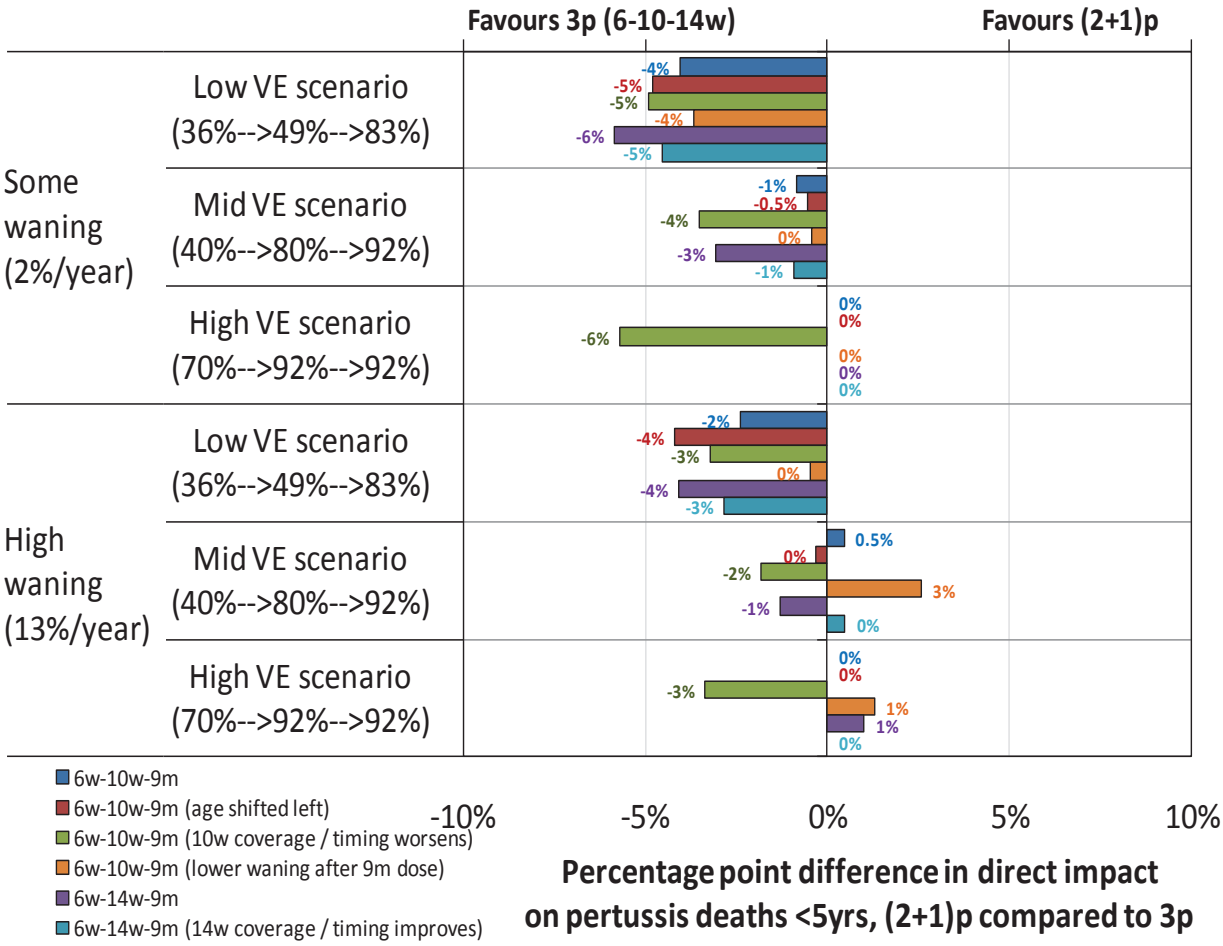
(ii) Secondly, it has been postulated that changing the schedule from 6-10-14w to 6w-10w-9m could adversely affect the coverage and timeliness of the existing 10w dose. If the timeliness and coverage were assumed to be similar to the 14w dose, only shifted 4 weeks earlier, then there would be a detrimental effect of changing to the 6w-10w-9m schedule – see scenario labeled '6w-10w-9m (10w coverage / timing worsens)';

(iii) Thirdly, one of the main reasons to delay the 3rd primary dose is to achieve a more durable immune response, and thus less waning. If a 25% lower waning rate were to be assumed after the 9m dose (vs the doses administered at 6-14w) then the 6w-10w-9m schedule would generally be preferable to the 6-10-14w schedule if 2 dose VE is high and waning is rapid – see scenario labeled '6w-10w-9m (lower waning after 9m dose)'. However, there is currently no evidence to support such an advantage, and indeed limited evidence that waning clinical protection occurs irrespective of whether a 3p or (2+1)p schedule is used – see Figure 11b;

(iv) Fourth, a 6w-14w-9m schedule was evaluated. This schedule generally had lower estimated direct impact than the 6w-10w-9m option because the 14w visit has worse coverage and timeliness than the 10w visit. However, with high VE and rapid waning this option could be slightly preferable to the 6w-10w-9m option; and,

(v) Finally, the 6w-14w-9m schedule was run under the assumption that timing and coverage of the 14w visit could be improved to reflect the coverage and timing of the 10w visit, labeled '6w-14w-9m (14w timing / coverage improves)'. In this scenario there was limited difference between the 6w-10w-9m schedule and the 6w-14w-9m schedule. Thus, the 6w-14w-9m option is unlikely to be a practical alternative to the current 6-10-14w schedule unless: a) there are substantial improvements in the coverage and timeliness of the 14w visit; and/or, b) there is a very significant clinical advantage of increasing the interval from 4 to 8 weeks. There is currently very limited evidence to support either of these assumptions.

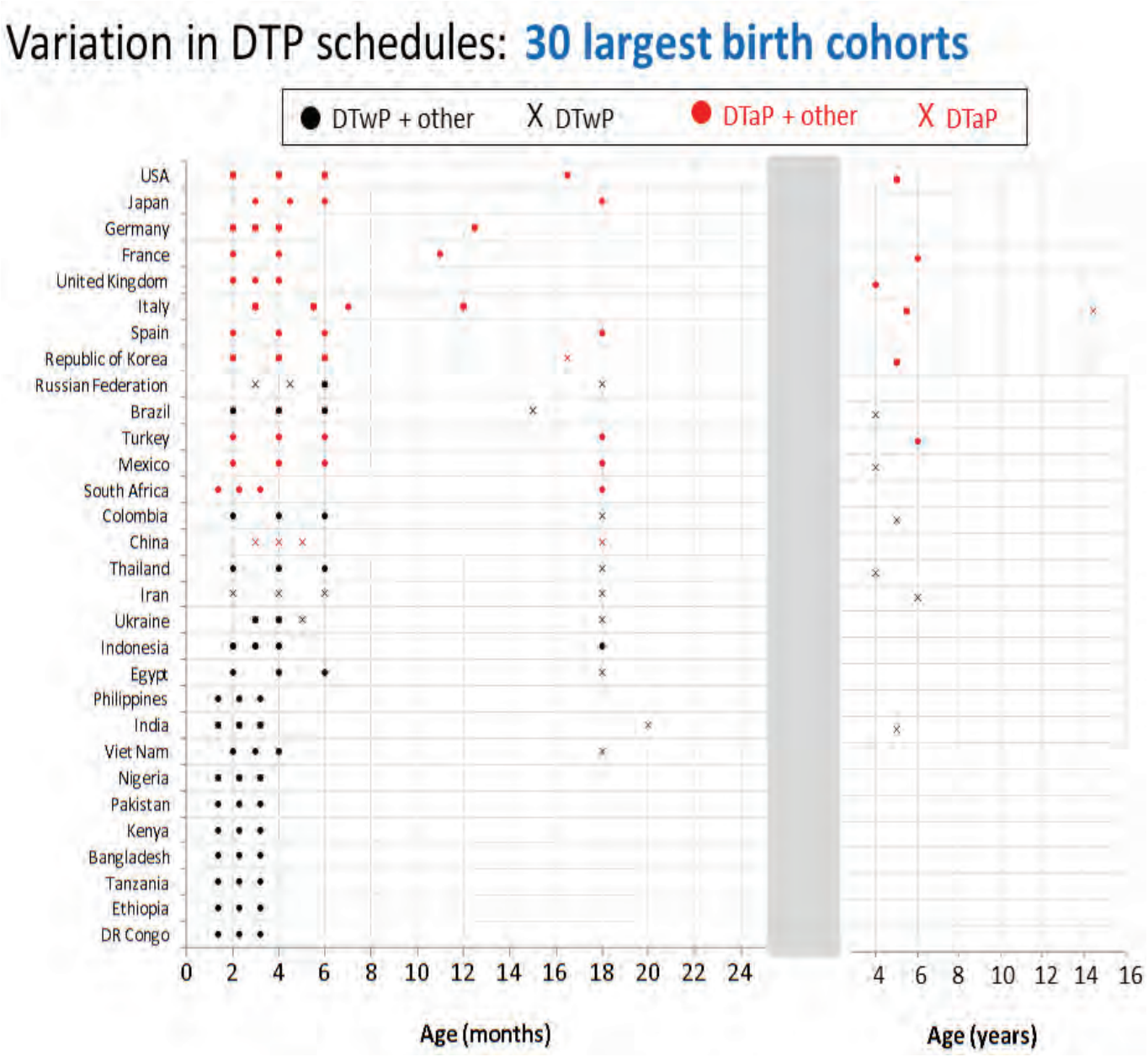
Figure. Percentage point difference* in direct impact against pertussis deaths in children <5yrs: (2+1)p compared to 3p in Senegal – alternative scenarios



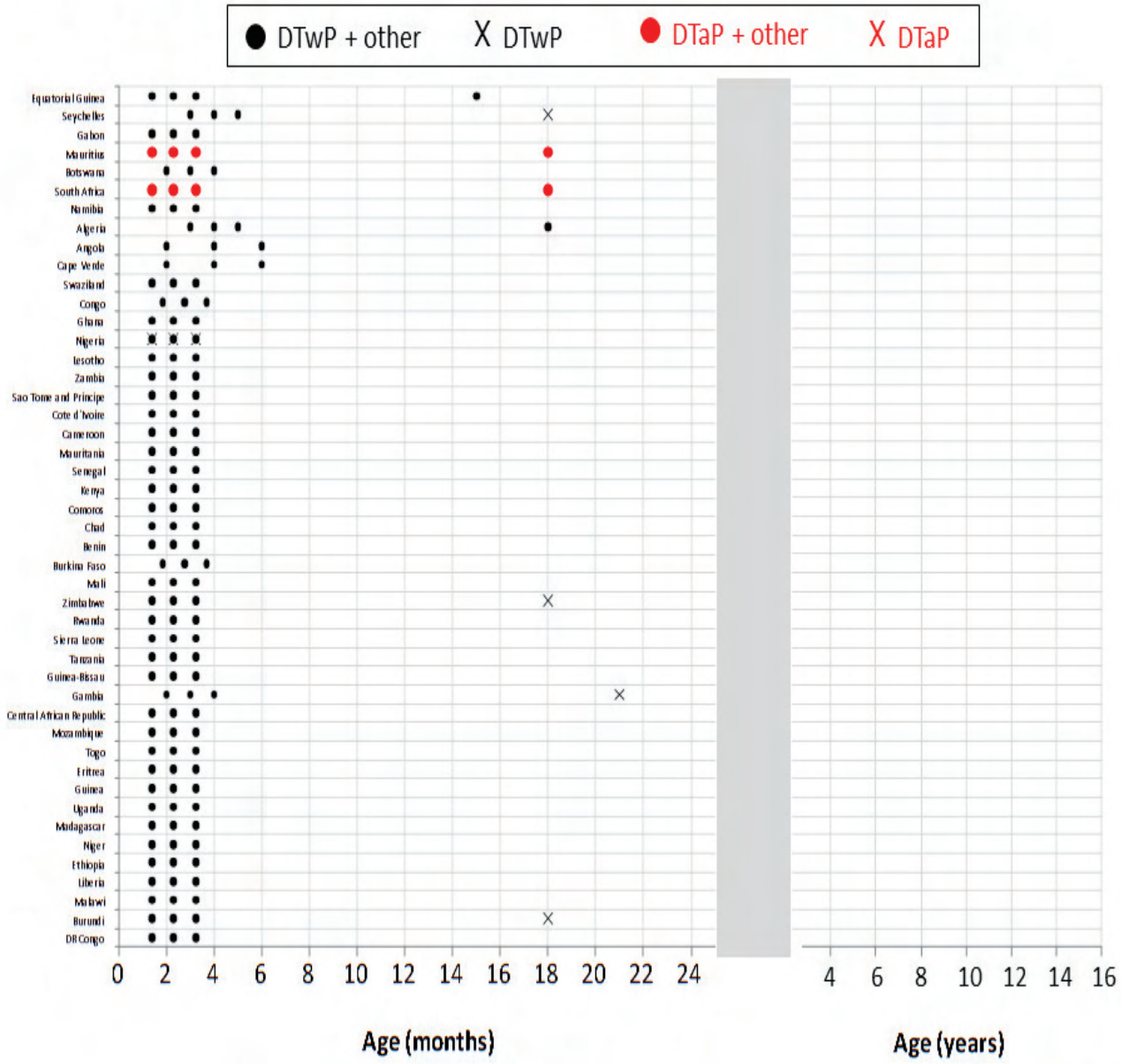
** Note. The direct impact of the 3p schedule is subtracted from the direct impact of the (2+1)p schedule to estimate the absolute (percentage point) difference in direct impact. Thus, positive differences indicate better direct impact with a (2+1)p schedule. Negative differences indicate better direct impact with the current 3p schedule*

In conclusion, there are large uncertainties around highly influential parameters included in the model (e.g. the rate of waning clinical protection) as well as uncertainties about the potential role of parameters that were not included (e.g. herd effects). In most scenarios which assume at least 80% protection after the 2nd dose (the midpoint assumed in this evaluation), a 6w-10w-9m schedule is likely to achieve better or similar direct impact to the existing 6-10-14w schedule. Thus, current evidence is not strong enough to preclude a move to a 6w-10w-9m schedule should this be advantageous for other antigens administered as part of the same combined vaccine. However, moving to a 6w-10w-9m schedule could be detrimental if 10w coverage and timeliness are adversely affected. Finally, 6w-14w-9m is likely to be inferior to 6w-10w-9m unless dramatic improvements can be achieved in the coverage and timing of the current 14w dose visit.

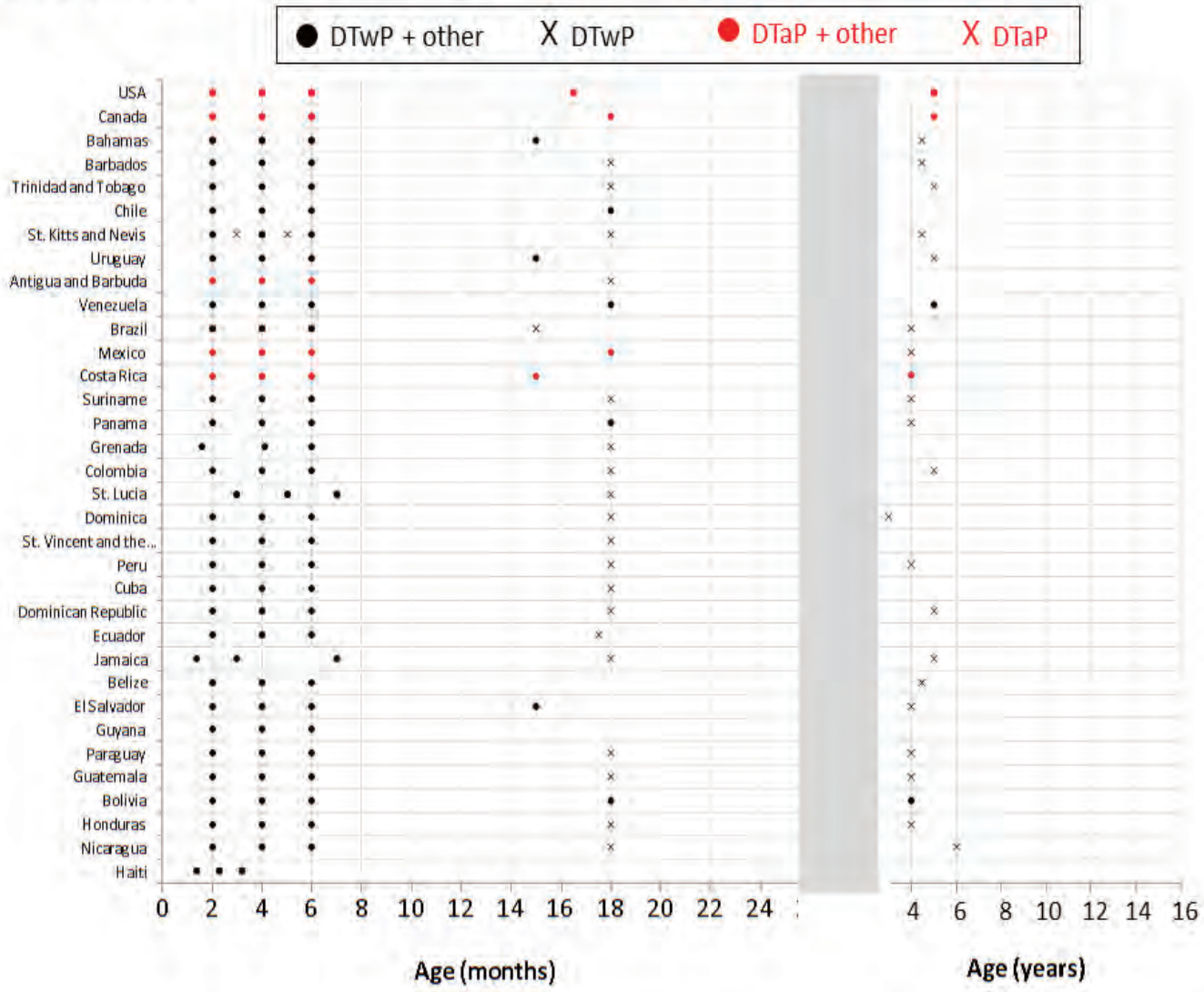
Appendix 5: **Current Pertussis vaccine schedules in the world**



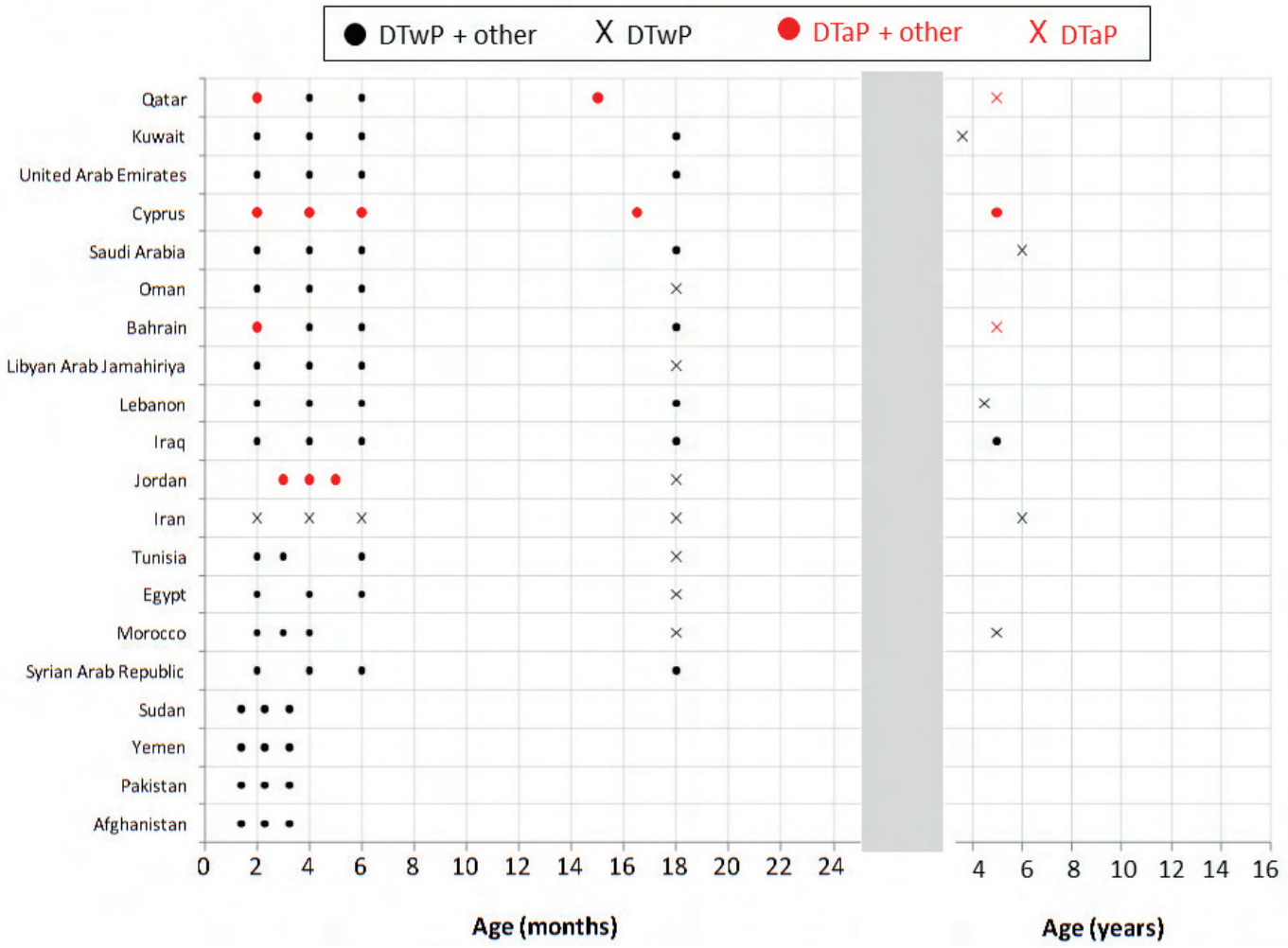
Variation in DTP schedules: Africa



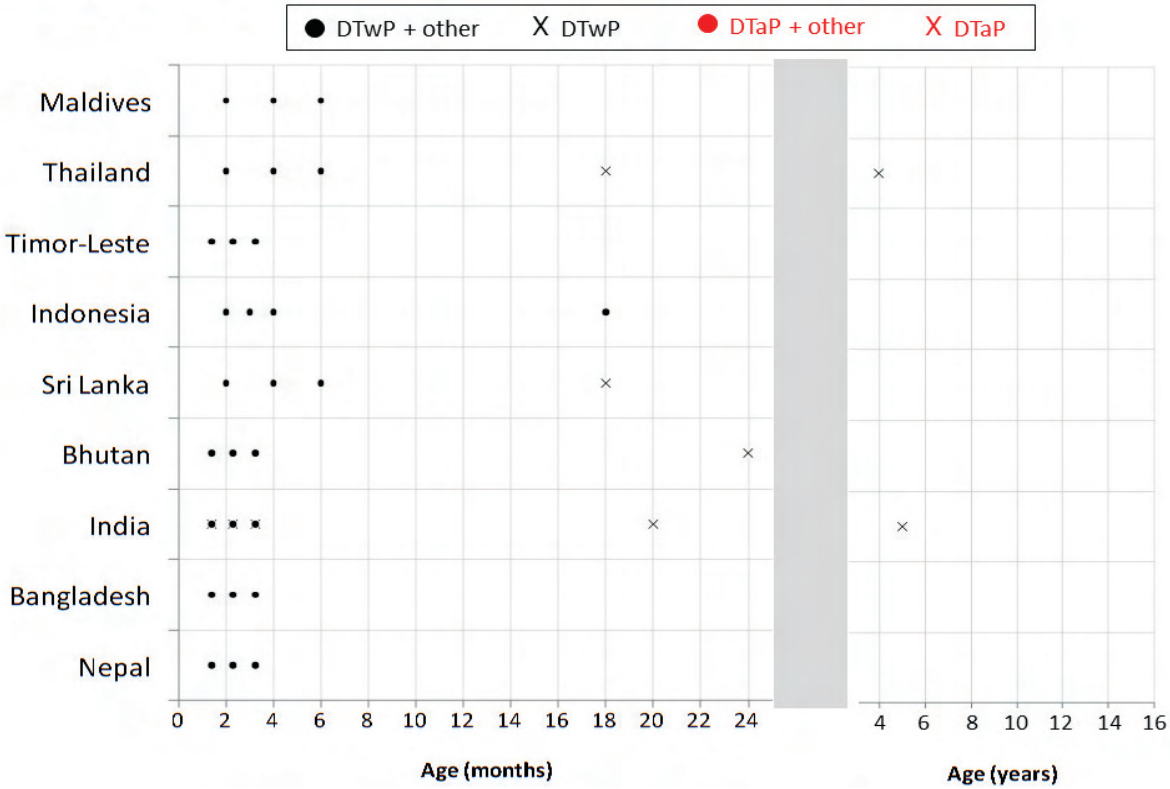
Variation in DTP schedules: Americas



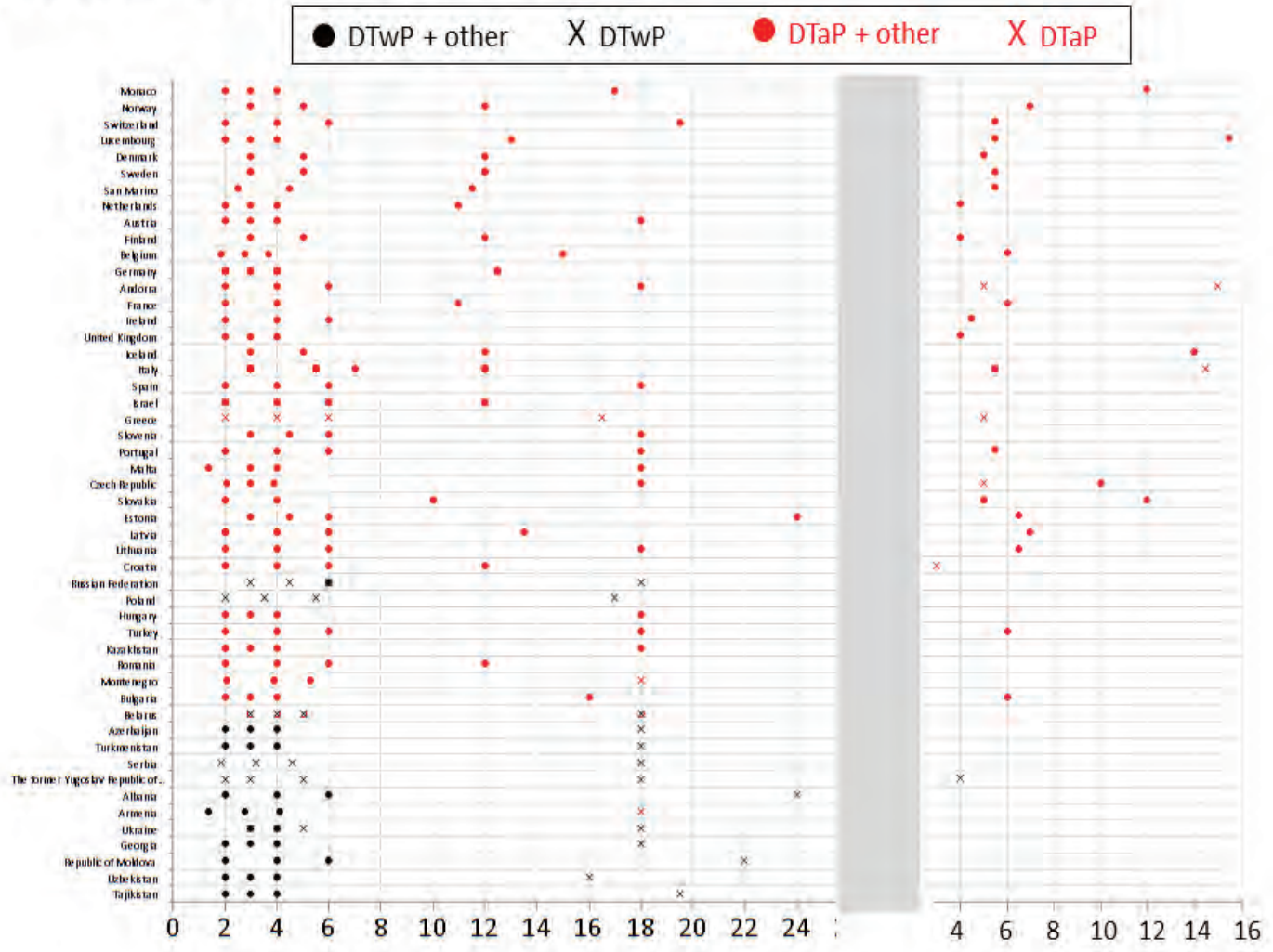
Variation in DTP schedules: Eastern Mediterranean



Variation in DTP schedules: South East Asia



Variation in DTP schedules: Europe



Variation in DTP schedules: Western Pacific