World Health Organization

Department of Immunization, Vaccines and Biologicals (IVB)

SAGE

April 2016

Strategic Advisory Group of Experts on Immunization
12 - 14 April 2016

Centre International de Conférences (CICG)
Geneva, Switzerland

World Health Organization

SAGE April 2016

This booklet contains key background documents for the meeting of the
Strategic Advisory Group of Experts (SAGE) on immunization
12 - 14 April 2016

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

http://www.who.int/immunization/sage/meetings/2016/april/en/

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Agenda
Meeting of the Strategic Advisory Group of Experts on Immunization (SAGE)
12 - 14 April 2016
Centre International de Conférences Genève (CICG), Geneva

Tuesday, 12 April 2016

Time	Session	Purpose of session, target outcomes and questions for SAGE	
8:30	**Welcome – introduction of participants** J. Abramson, Chair of SAGE.		20 min.
8:50	**Report from Director, IVB - Session 1** Global report including key updates and challenges from regions. J.-M. Okwo-Bele, WHO. 30 min. Discussion. 1h 30 min.	**FOR INFORMATION**	2h
10:15	**Coffee/tea break**	**Break**	**30 min.**
10:45	**Report from Director, IVB - Session 1, contd.** Discussion contd.		
11:20	**Report from Gavi, the Vaccine Alliance - Session 2** Report from Gavi, the Vaccine Alliance. S. Berkley, Gavi, the Vaccine Alliance. 20 min. Discussion. 20 min.	**FOR INFORMATION**	40 min.
12:00	**Reports from other Advisory Committees on Immunization - Session 3** Report of the Global Advisory Committee on Vaccine Safety (GACVS). R. Pless, Chair of GACVS. 10 min. Discussion. 10 min.	**FOR INFORMATION**	20 min.
12:20	**Lunch**	**Break**	**1h 30 min.**

13:50	**Respiratory Syncytial Virus Vaccines (RSV) - Session 4** Summary of global epidemiology and disease burden estimates for RSV. H. Nair, University of Edinburgh. 10 min. Discussion. 10 min. Background to RSV active/passive immunization development, and status of leading candidates. R. Karron, Johns Hopkins Bloomberg School of Public Health. 20 min. Discussion. 20 min. WHO consultations in 2015-2016 on RSV active/passive immunization. V. Moorthy, WHO. 15 min. Discussion. 15 min.	**FOR INFORMATION** Update SAGE on the current status of development of RSV vaccines. Give SAGE an opportunity for any input that the group would like to contribute at this stage of vaccine development, noting that one candidate is in Pivotal Phase 3, and the pipeline is very active.	1h 30 min.
15:20	**Coffee/tea break**		**30 min.**
15:50	**Global polio eradication initiative - Session 5** Objective of the session and overview of Global Polio Eradication Initiative. M. Zaffran, WHO. 20 min. Updates on implementation of OPV2 withdrawal. D. Chang-Blanc, WHO. 20 min. Discussion. 20 min. Report from SAGE Polio WG. Y. AL-Mazrou, Chair of the Polio WG. 20 min. o Summary of WG meeting o Future immunization policy: Issues, way forward Discussion. 70 min.	**FOR INFORMATION AND DISCUSSION** To update SAGE on the: • current status of the polio eradication program • status of implementation of OPV2 withdrawal • issues and timelines for discussions on future immunization policy after OPV withdrawal SAGE is asked to discuss the use of fractional ID IPV for campaign and routine immunization.	2h 30 min.
18:20	**Cocktail**		

Wednesday, 13 April 2016

08:30	**Implementation in the context of health system strengthening (HSS) and universal health coverage- Session 6** Introduction of the session. N. Turner, Member of SAGE. 5 min. Presentation on the role of HSS in achieving sustainable and effective impact including achieving economies of scale and improved quality and greater equity of coverage. M.-P. Kieny, WHO. 15 min. Discussion. 40 min. Presentation of selected topics on implementation programme design including integrated supply chain management, quality data on service delivery and coordinated planning of services and examples of fragile states. H. Karamagi, WHO. 20 min. Discussion. 40 min.	**FOR INFORMATION AND DISCUSSION** Inform SAGE on adapting immunization services and provision to support integrated service delivery as part of the health system to achieve universal health coverage. The session will provide an overview of the health systems, complexity and immunization. It will address key experiences related to implementation of vaccines and financial efficiency and gains. Based on experience from Ebola, will highlight importance of resilience and lessons learnt. SAGE will be asked to provide feedback. This input will be used to define an operations research agenda on a systems based approach for improving immunization coverage and closing equity gaps..	2h
10:30	**Coffee/tea break**	**Break**	**30 min.**
11:00	**Preempting and responding to vaccine shortages - Session 7** Introduction of the session. C-A. Siegrist, Member of SAGE. 15 min. Dealing with vaccine shortages: current situation and ongoing activities. 1. Impact of shortages and solutions set up by countries. O. Benes. WHO. 15 min. 2. Global operational procurement planning and long-term strategic supply security. A. Ottosen, UNICEF. 20 min. 3. Vaccine shortages: Improving cooperation, communication and management in the European Union. M. Sulzner, European Commission Directorate-General for Health and Food Safety. 10 min. Discussion. 60 min.	**FOR INFORMATION AND DISCUSSION** Present SAGE with a review of the current situation of vaccine shortages, reasons for shortages as well as elements that increase their risk. Present SAGE with activities that are already being put in place at the national, regional and global levels to mitigate the impact of shortages and pre-empt them. SAGE will be requested to provide guidance to WHO regarding activities that need to be continued, strengthened or explored to better pre-empt and respond to global shortages, particularly within the scope of the WHA68.6 resolution - conditional to the need for additional resources if further activities were to be implemented.	2h
13:00	**Lunch**	**Break**	**1h**

14:00	**Missed opportunities for vaccination - Session 8** Introduction to the topic. C. Wiysonge, Member of SAGE. 10 min. Results of two country missed opportunities for vaccination assessments in Africa. B. Anya, WHO. 15 min. Status of missed opportunities for vaccination assessments in the Americas. M. Velandia, WHO. 15 min. WHO Global Plan of Action for Improving Coverage and Equity by Scaling Up Missed Opportunities Interventions. I. Ogbuanu, WHO. 20 min. Discussion. 60 min.	**FOR INFORMATION AND DECISION** SAGE will be: • Provided with an update on ongoing work to address missed opportunities for vaccination • Presented with the potential value and impact of the updated approach for assessing extent of, and implementing solutions to reduce missed opportunities for vaccination • Requested to endorse the updated approach for reducing missed opportunities • Asked to advise on the proposed framework for addressing missed opportunities and on the partner coordination mechanisms	2h
16:00	**Coffee/tea break**		**30 min.**
16:30	**Second year of life platform - Session 9** Introduction to the topic. J. Jawad, Member of SAGE. 10 min. Activities towards developing guidance for a Second-Year-of-Life (2YL) healthy child visit. R. Eggers, WHO. 15 min. Discussion. 30 min. Findings of the Zambia 2YL case study. R. Fields, John Snow, Inc.. 15 min. Landscape analysis on 2YL. I. Mirza, UNICEF. 15 min. Discussion. 30 min.	**FOR INFORMATION AND DISCUSSION** To inform SAGE and immunization partners about the development of guidance to establish a second year of life health child visit that includes vaccination. Aim is to inform SAGE on the justification for the needs and opportunities of a healthy child visit in the second year of life and provide an understanding of the proposed work and outcomes of this project. SAGE will be asked to provide input to the process and/or content**.**	2h
18:30	**End of day**		

Thursday, 14 April 2016

08:30	**Dengue vaccine - Session 10** Introduction. J. Farrar, Wellcome Trust, Co-Chair of SAGE Working Group on Dengue vaccine. 15 min. Dengue vaccine clinical trial results. S. Thomas, US Walter Reed Army Institute of Research. 30 min. Discussion. 20 min. Comparative modelling of dengue vaccine impact, N. Ferguson, Imperial College, London. 20 min. Discussion. 15 min.	**FOR DECISION** Present SAGE with the report of the SAGE Working Group on Dengue Vaccines and Vaccination on the CYD dengue vaccine and request SAGE's consideration of the proposed recommendations. SAGE recommendations on vaccine use will then be used to write the first WHO position paper on the use of a dengue vaccine.	3h
10:10	**Coffee/tea break**	**Break**	**30 min.**
10:40	**Dengue vaccine - Session 10, contd.** Dengue Vaccines Working Group assessment and proposed recommendations. T. Nolan, SAGE member and Co-Chair of SAGE Working Group on Dengue vaccine. 20 min. Discussion. 60 min.		
12:00	**Closing**		20 min.
12:20	**End of meeting**		

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

SAGE members

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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 vaccination policies and strategies, ranging from vaccines and technology, research and development, to delivery of vaccination and its linkages with other health interventions. SAGE's remit extends to the control of all vaccine-preventable diseases as part of an integrated, people centred platform of disease prevention that spans the human life-course and in the context of health systems strengthening.

SAGE advises the WHO Director-General specifically on the:

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

Membership

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

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

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

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

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

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

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

Prior to being considered for SAGE membership, nominees shall be required to complete a WHO Declaration of Interests form as per the attached form (Annex 1).

All papers presented to SAGE, which may include pre-publication copies of research reports or documents of commercial significance, shall be treated as confidential. SAGE deliberations are confidential and may not be publicly disclosed by SAGE members. Therefore, prior to confirmation by WHO of their appointment as SAGE members, SAGE nominees shall be required to sign a Confidentiality Undertaking (Annex 2).

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

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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 or involvement in activities resulting in a conflict of interest incompatible with serving on SAGE; and
3. a lack of professionalism involving, for example, a breach of confidentiality.

Meetings and operational procedures

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

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

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

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

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

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

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

Roles and responsibilities of SAGE members

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

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

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

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

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

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

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

SAGE Working Groups are established as resources intended to increase the effectiveness of SAGE deliberations by reviewing and providing evidence-based information and options for recommendations together with implications of the various options to be discussed by SAGE during one of its biannual meetings. These Working Groups are normally established on a time-limited basis to help address specific questions identified by SAGE when the issue is particularly complicated or time-consuming and could not be addressed by an existing standing WHO advisory committee. The need and charge for a Working Group is discussed and agreed during SAGE meetings. The purpose, structure and functioning of the Working Groups is described in detail in Annex 3 (Purpose, structure and functioning of the Strategic Advisory Group of Experts on Immunization (SAGE) Working Groups).

For its proceedings, SAGE shall follow an evidence-based review process as outlined in the SAGE guidance document on evidence-based vaccine-related recommendations (http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf?ua=1).

More detailed information on SAGE operating procedures is available on the SAGE website (http://www.who.int/immunization/sage/working_mechanisms/en/).

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

Purpose and decision to establish a SAGE Working Group

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

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

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

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

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

Working Group composition and selection of membership

Each Working Group should include two or more SAGE members (one of whom functions as Chair), and additional subject matter experts serving in their own individual capacity and with a view to meet the identified needed expertise for the group. SAGE members and other experts who have identified conflicts of interest cannot serve on the Working Group charged with responsibility in the identified areas of conflict. WHO staff (one of whom functions as the Working Group technical lead serve as secretariat to the Working Group. In some instances other UN or non UN agencies can be co-opted as part of the secretariat. For Working Groups which terms of reference require proceedings over a number of years, if a SAGE member rotates out of SAGE while the Working Group is still active, then he/she remains on the Working Group but a new SAGE member should be enrolled to serve on the group. A new SAGE member should be appointed as Working Group Chair when the previous Chair rotates out of SAGE. For Working Groups having proceedings spanning over a number of years, the same rotation process as applied to SAGE membership should be applied i.e. two 3–year terms, the renewal being determined by the Working Group Chair, Lead WHO technical staff and SAGE Executive secretary based on the contribution of the member to the group. If some members resign for personal reasons, are no longer eligible to serve on the group, or are unable to meaningfully contribute to the proceedings of the group, they can be replaced with first considering an appointment from the list of initial candidates to join the group. The decision will be made as for the selection of candidates (see below). If no one from this list is suitable then another expert could be solicited and co-opted without resourcing to an open call for nomination.

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

A public call for nomination for Working Group members will be posted on the SAGE website together with the relevant TORs of the Working Group and indication of the desirable expertise. SAGE members, regional offices, diplomatic missions, WHO staff and key partner organizations will also be approached for potential nominations. Nominees will be requested to provide both a Curriculum Vitae and a completed Declaration of Interests form prior to being considered for membership on the Working Group. From the pool of nominees, the Working Group Chair, SAGE Executive Secretary and Lead WHO staff will propose a Working Group composition for endorsement by the SAGE Chair and the Director of the Department of Immunization, Vaccines and Biologicals. The proposed list should be accompanied by the rationale for the proposed selection. In addition to meeting the required expertise, attention will be given to ensure proper diversity including geographic and gender representation. Chairs of regional technical immunization advisory groups are not eligible to serve on SAGE Working Groups.

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

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

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Working Group Process

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

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

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

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

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

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

Individuals other than Working Group members and the Secretariat may participate in Working Group meetings only if their contribution is required by the Working Group. These may include organization representatives, industry representatives/experts, public health officials, faculty staff of academic institutions or other experts. These experts are excluded from any discussions and deliberations within the Working Group and are solely invited to provide specific requested information on a predefined topic. Observers are not allowed to attend Working Group proceedings.

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

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

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Management of Conflict of Interest

The value and impact of SAGE recommendations and WHO policy recommendations are critically dependent upon public trust in the integrity of the process. Reported interests are assessed and managed according to SAGE procedures. Summarized Declarations of Interest are publicly posted on the SAGE website in conjunction with the Working Group's TORs and composition (http://www.who.int/immunization/sage/working_mechanisms/en/). Members are expected to proactively inform WHO on any change in relevant interests. The posted summary will then be updated accordingly.

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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

- Yagob Al-Mazrou, (Chair of the Working Group since September 2015), Secretary General - Health Services Council of the Kingdom of Saudi Arabia, Saudi Arabia.
- Peter Figueroa, University of the West Indies, Jamaica, (Chair of Working Group until August 2015 and SAGE member until April 2015).
- 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, SAGE member until August 2015).
- Elizabeth Miller, Health Protection Agency, United Kingdom, (Chair of the Working Group until February 2014 and SAGE member until November 2013).

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.

Updated: March 2016

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

Terms of Reference

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

Composition

SAGE Members

- Narendra Arora (Chair of the Working Group since September 2015), International Clinical Epidemiology Network, India.
- Ilesh Jani, Instituto Nacional de Saúde (National Institute for Health), Mozambique (Member of the Working Group since October 2015).
- Nikki Turner, General Practice and Primary Care, University of Auckland, New Zealand (Member of the Working Group since October 2015).
- Hyam Bashour, changed as of February 2013 - retired from Department of Family and Community Medicine, Damascus University, Syria (SAGE member until April 2011).
- David Durrheim, Hunter New England Area Health Service and Professor of Public Health, Australia (SAGE member until April 2012).
- Peter Figueroa, University of the West Indies, Jamaica, (Chair of Working Group until August 2015 and SAGE member until April 2015).
- Helen Rees, University of Witwatersrand, South Africa (SAGE member until August 2013).

Experts

- Natasha Crowcroft, Surveillance and Epidemiology, Public Health Ontario, Canada.
- William Moss, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.
- Susan Reef, Global Immunization Division, Centres for Disease Control and Prevention, USA.
- El Tayeb Ahmed El Sayed, Federal Ministry of Health, Sudan (resigned from the Working Group May 2012).
- Heidi Larson, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, United Kingdom (resigned from the Working Group February 2015).
- Pier Luigi Lopalco, European Centre for Disease Prevention and Control, Sweden (resigned from the Working Group February 2015).
- Makoto Takeda, Department of Virology, National Institute of Infectious Diseases, Japan (resigned from the Working Group in September 2015).

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

Terms of Reference

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

Specifically, the WG will:

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

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

Composition

SAGE Members

- Narendra Arora, (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.
- Alejandro Cravioto, Senior Epidemiologist, Global Evaluative Sciences, Seattle, USA (as of February 2015 and previously Chief Scientific Officer, International Vaccine Institute, Seoul Republic of Korea) (SAGE member since October 2015.
- Helen Rees, Executive Director - Reproductive Health Research Unit, University of Witwatersrand, South Africa (SAGE member until August 2013).
- David Salisbury, Associate Fellow, Centre on Global Health Security, Chatham House, London, UK (affiliation as of January 2014 and previously Director of Immunization, Department of Health, UK and SAGE member until 2010).

Experts

- Fuqiang Cui, Epidemiology Professor, Deputy Director National Immunization Program, China CDC, China.
- Elizabeth Ferdinand, Associate Lecturer, University of the West Indias – Cave Hill, Barbados (affiliation as of January 2015 and previously Senior Medical Officer of Health and EPI Manager, Barbados).
- Alan Hinman, Senior Public Health Scientist - Task Force for Global Health, USA.
- Stephen Inglis, Director National Institute Biological Standards & Control, Health Protection Agency, UK.
- Marie-Yvette Madrid, Independent Consultant, Geneva, Switzerland (as of June 2014 to replace Shawn Gilchrist).
- Amani Mahmoud Mustafa, Project Manager, Sudan Public Health Training Initiative, The Carter Centre, Sudan (affiliation as of May 2014 and previously EPI Manager, Ministry of Health, Sudan).
- Rebecca Martin, Director Global Immunization Division, US CDC, USA.
- Rozina Mistry, Lecturer and Course Director, Aga Kahn University, Pakistan.
- Shawn Gilchrist, President S Gilchrist Consulting Services Inc., Canada (resigned from the Working Group May 2014 and replaced by Yvette Madrid).

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

Terms of Reference

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

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

- 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

- Rees, Helen, (Co-Chair of the Working Group, Chair of the African Task Force on Immunization (TFI) Executive Director -Reproductive Health Research Unit, University of Witwatersrand, South Africa (SAGE member until August 2013).
- Were, Fred, (Co-Chair of the Working Group from March 2016) Executive Director - Professor, Department of Paediatrics and Child Health, University of Nairobi, Kenya.
- O'Brien, Kate, Professor, Department of International Health & Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, USA.
- Tomori, Oyewale, (Co-Chair of the Working Group until February 2016), Professor of Virology, Redeemer's University, Nigeria; (SAGE member until April 2015).
- Wiysonge, Charles, (Chair of the African Task Force on Immunization (TFI)), Professor in Community Health Stellenbosch University; Deputy Director Centre for Evidence-based Heath Care Stellenbosch University, South Africa.

Experts

- 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.
- 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. / Public Health Capacity and Communication Unit, European Centre for Disease Control, Sweden.

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 (GAVCS) until February 2016)

Updated: March 2016

- Pless, Robert; replaces previous Chair Melinda Wharton as of March 2016 (Chair of WHO Global Advisory Committee on Vaccine Safety (GACVS)).

5. 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 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:

1. the global prevalence and burden of disease caused by dengue
2. the safety, efficacy, and immunogenicity profile of licensed dengue vaccines
3. the schedule, age of administration, and potential vaccination strategies for dengue vaccines, including setting-specific attributes that may be important for designing immunization programs
4. the disease impact and cost-effectiveness of dengue immunization programs
5. 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.
6. 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, National Immunization Program, Ministry of Public Health, Nonthaburi, Thailand.

Experts

- Jeremy Farrar, (Co-Chair of the Working Group), Wellcome Trust, UK.
- Amanda Amarasinghe, Ministry of Health, Sri Lanka.
- Alan Barrett, University of Texas Medical Branch, USA.
- Anna Durbin, Johns Hopkins Bloomberg School of Public Health, USA.
- Elizabeth Ferdinand, Ministry of Health, Barbados (Retired).
- Maria Guzman, Pedro Kouri Tropical Medicine Institute, Cuba.
- 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.
- Stephen Thomas, Walter Reed Army Institute of Research, USA.

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

Terms of reference

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

Composition

SAGE members

- Kari Johansen (Chair of the Working Group), Expert in Vaccine Surveillance and Response Support Unit, European Centre for Disease Prevention and Control, Sweden.
- Jaleela Sayed Jawad, Head of the immunization group, Ministry of Health, Kingdom of Bahrain.
- Charles Wiysonge, Deputy Director, Centre for Evidence-based Heath Care and Professor in Community Health, Stellenbosch University, South Africa.

Experts

- Bradford Gessner, Scientific Director, Agence de Médecine Preventive, France.
- Ardi Kaptiningsih, previously served as Regional Adviser, Making Pregnancy Safer, Women and Reproductive Health, WPRO, Philippines.
- Rakesh Kumar, Joint Secretary and Director, Ministry of Health & Family Welfare, India.
- Elizabeth Mason, previously served as Director of the Department of Maternal, Newborn, Child and Adolescent Health, WHO, Switzerland.
- Elizabeth Miller (SAGE member from 2007-2013), Consultant Epidemiologist, Immunisation Department, Health Protection Agency, Centre for Infections, United Kingdom.
- Tony Nelson, Professional Clinical Consultant, Department of Paediatrics, The Chinese University of Hong Kong.
- Alexis Ntabona, Consultant for ExpandNET, Democratic Republic of the Congo.
- Robert Steinglass, Director Immunization Centre and Leader for the Maternal and Child Survival Program, John Snow, Inc., USA.

Updated: March 2016

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

Terms of reference

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

Composition

SAGE Members

- Alejandro Cravioto, (Chair of the Working Group) Chief Scientific Officer, Global Evaluative Sciences, Inc., in Seattle, Washington, USA
- Jaleela Sayed Jawad, Head of the immunization group, Ministry of Health, Kingdom of Bahrain.

Experts

- Dang Duc Anh, Director, National Institute of Hygiene and Epidemiology, Hanoi, Vietnam.
- Asma Yaroh Gali, General Director of Ministry of Public Health and Ambassador for the Campaign on Accelerated Reduction of Maternal Mortality in Africa, Niamey, Niger.
- Rebecca Grais, Director Research, Epicentre, Paris, France.
- Louise Ivers, Associate Professor, Division of Global Health Equity, Harvard Medical School Boston, USA.
- Francis Javier Alcalde Luquero, Associate Scientist, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA.
- Firdausi Qadri, Director, Centre for Vaccine Sciences, International Centre for Diarrhoeal Disease Research, Bangladesh.
- Cynthia Sema, Head of Department, National Institute of Health Ministry of Health, Maputo, Mozambique.
- Dipika Sur, previously National Institute of Cholera and Enteric Diseases, Kolkata, India.
- Thomas Wierzba, Enteric Vaccine Initiative Vaccine Development Global Program, PATH, Washington, USA.

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

Terms of reference

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

Specifically, the Working Group will review evidence on:

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

Composition

SAGE Members

- Ilesh Jani (Chair of the Working Group), Instituto Nacional de Saúde (National Institute for Health), Mozambique.
- Narendra Arora, International Clinical Epidemiology Network, India.
- Kari Johansen, European Centre for Disease Prevention and Control, Sweden.

Experts

- Zulfiqar A. Bhutta, (SickKids Center for Global Child Health, The Hospital for Sick Children, Canada; Center of Excellence in Women and Child Health, Aga Khan University, Pakistan
- John A. Crump, Centre for International Health, Department of Preventive and Social Medicine, University of Otago, New Zealand
- Myron M. Levine, Department of Medicine; and Center for Vaccine Development, University of Maryland, USA
- Dafrossa Lyimo, National EPI Manager (Dar es Salaam), Tanzania
- Florian Marks, Department of Epidemiology, International Vaccine Institute, Republic of Korea)
- Mark A. Miller (Office of the Director; and Division of International Epidemiology and Population Studies, National Institutes of Health, USA
- Christopher M. Parry, School of Tropical Medicine and Global Health, University of Nagasaki, Japan; and London School of Hygiene and Tropical Medicine, UK
- Richard A. Strugnell, Department of Microbiology and Immunology, University of Melbourne, Australia)
- Dipika Sur (Consultant, Translational Health Science and Technology Institute, India

Updated: March 2016

Strategic Advisory Group of Experts on Immunization meeting
12 - 14 April 2016
Geneva, Switzerland

Provisional list of participants as of 18 March 2016

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World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

11 DECEMBER 2015, 90th YEAR / 11 DÉCEMBRE 2015, 90e ANNÉE
No. 50, 2015, 90, 681–700
http://www.who.int/wer

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Meeting of the Strategic Advisory Group of Experts on immunization, October 2015 – conclusions and recommendations

The Strategic Advisory Group of Experts on immunization (SAGE)[1] met on 20–22 October 2015. This report summarizes the discussions, conclusions and recommendations.[2] For the malaria session, SAGE was joined by the Malaria Policy Advisory Committee (MPAC) and the conclusions and recommendations concerning malaria vaccine are those of both committees.

Report from the WHO Department of Immunization, Vaccines and Biologicals

The core message of the report, "closing the immunization gap", is reflected in most of the following activities.

The report addressed vaccine research coordinated by WHO, highlighting unprecedented contributions in the development of Ebola vaccines, emphasizing collaborative efforts, adaptation of traditional research and development models, compressed timeframes and innovative partnerships. The report flagged the Global Vaccine & Immunization Research Forum,[3] which will be held in March 2016.

The report highlighted global progress made on increasing vaccination coverage including reaching 90% coverage with the first dose of diphtheria-tetanus-pertussis (DTP) containing vaccine globally.

[1] See http://www.who.int/immunization/policy/sage/en/; accessed October 2015.

[2] The complete set of presentations and background materials used for the SAGE meeting of 20–22 October 2015 together with the list of SAGE members and the summarized declarations of interests provided by SAGE members are available at http://www.who.int/immunization/sage/meetings/2015/october/en/index.html; accessed October 2015.

[3] See http://www.who.int/immunization/research/forums_and_initiatives/gvirf/en/.

Réunion du Groupe stratégique consultatif d'experts sur la vaccination, octobre 2015 – conclusions et recommandations

Le Groupe stratégique consultatif d'experts sur la vaccination (SAGE)[1] s'est réuni du 20 au 22 octobre 2015. Le présent rapport résume les discussions, conclusions et recommandations auxquelles il est parvenu.[2] Le Comité de pilotage de la politique de lutte antipaludique (MPAC) s'est joint au SAGE pour la session consacrée au paludisme: les conclusions et recommandations relatives au vaccin antipaludique émanent donc de ces deux Comités.

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

Ce rapport est essentiellement axé sur la nécessité de combler les lacunes de la couverture vaccinale, message qui est reflété dans la plupart des activités mentionnées ci-dessous.

Le rapport évoque les travaux de recherche vaccinale coordonnés par l'OMS, soulignant les contributions sans précédent apportées au développement des vaccins contre Ebola, dans un contexte de collaboration, d'adaptation des modèles traditionnels de recherche et développement, de compression des délais et d'établissement de partenariats novateurs. Il indique en outre que le Forum mondial de recherche sur les vaccins et la vaccination[3] se tiendra en mars 2016.

Le rapport souligne les progrès réalisés dans le monde entier en matière de couverture vaccinale, notant en particulier que la couverture par la première dose du vaccin antidiphtérique-antitétanique-anticoquelucheux (DTC)

[1] Voir http://www.who.int/immunization/policy/sage/fr/: consulté en octobre 2015.

[2] La série complète des communications et des documents de travail utilisés pour la réunion du SAGE du 20 au 22 octobre 2015, ainsi que la liste des membres du SAGE et les résumés de leurs déclarations d'intérêts sont disponibles à l'adresse: http://www.who.int/immunization/sage/meetings/2015/october/en/index.html: consulté en octobre 2015.

[3] Voir http://www.who.int/immunization/research/forums_and_initiatives/gvirf/en/.

WORLD HEALTH ORGANIZATION
Geneva

ORGANISATION MONDIALE DE LA SANTÉ
Genève

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

12.2015
ISSN 0049-8114
Printed in Switzerland

However the need to continue efforts to reduce drop-out between the first and third doses of DTP (86% vaccination coverage in 2014) was emphasized. Further, 10 years after SAGE recommended the use of newer vaccines such as rotavirus and pneumococcal conjugate vaccine (PCV), vaccination coverage rates remain very low (below 35% worldwide, which in addition to coverage issues reflects the delayed vaccine introductions particularly in large countries).

a atteint un taux de 90% à l'échelle mondiale. Il insiste toutefois sur la nécessité de poursuivre les efforts entrepris pour réduire le taux d'abandon de la vaccination entre la deuxième et la 3e dose de DTC (couverture vaccinale de 86% en 2014). Le rapport constate par ailleurs que 10 ans après la recommandation du SAGE plaidant en faveur de l'administration de nouveaux vaccins, tels que le vaccin antirotavirus et le vaccin antipneumococcique conjugué (VPC), la couverture vaccinale correspondante demeure très faible (inférieure à 35% à l'échelle mondiale, ce qui résulte non seulement de problèmes de couverture, mais aussi d'une introduction tardive du vaccin, en particulier dans les pays de grande taille).

The report stressed that checking vaccination cards should be the norm whenever children are seen at health-care facilities for well-child care or sick visits. Exit interviews conducted in 2015 at health facilities in Chad and Malawi identified large numbers of missed opportunities for vaccination. Of the children attending the facilities, 75% did not receive the vaccines for which they were eligible. Among children attending for medical consultation or another reason than for a medical consultation or vaccination visit, 95% and 96% respectively were not vaccinated despite being eligible for one or more vaccines. SAGE applauded the work on missed opportunities which should help reinforce the integration of immunization in health systems of all countries.

Le rapport souligne que la vérification du carnet de vaccination devrait être systématique lorsqu'un enfant en bonne santé se présente dans un établissement de soins, que la consultation soit liée à une maladie ou à une simple visite médicale. Des enquêtes menées à la sortie d'établissements de santé au Tchad et au Malawi en 2015 ont révélé un nombre important d'occasions manquées en matière de vaccination. Sur tous les enfants qui avaient visité un centre de soins, 75% en sont ressortis sans avoir reçu les vaccins auxquels ils pouvaient prétendre. Parmi les enfants qui s'étaient présentés pour une consultation médicale ou ou pour une autre raison qu'une consultation médicale ou une visite de vaccination, 95% et 96% respectivement n'avaient pas été vaccinés bien que remplissant les critères d'administration d'au moins un vaccin. Le SAGE a salué les efforts déployés pour remédier aux opportunités manquées, efforts qui devraient permettre une meilleure intégration de la vaccination dans les systèmes de santé de tous les pays.

Despite challenges imposed by Ebola, including for routine immunization coverage, the African Region achieved historic milestones towards certification of polio-free status with the removal of Nigeria from the list of polio-endemic countries; hence there is now no polio-endemic country in Africa. Important progress was made in the Region by introducing rotavirus vaccine as well as PCV. Strengthening routine immunization services remains difficult, including in GAVI-graduating countries.

Malgré les défis imposés par la maladie à virus Ebola, notamment en termes de couverture de la vaccination systématique, la Région africaine a franchi une étape historique vers l'obtention de la certification de région exempte de poliomyélite: le Nigéria a été retiré de la liste des pays d'endémie de la poliomyélite, ce qui signifie que l'Afrique ne compte plus aucun pays d'endémie. L'introduction du vaccin antirotavirus et du VPC a constitué un progrès important pour la région. Le renforcement des services de vaccination systématique demeure difficile, y compris dans les pays qui se qualifient au titre de l'Alliance GAVI.

SAGE applauded the Region of the Americas on achieving the key milestone of rubella elimination in August 2015, and Brazil on the ending of measles transmission in the country. SAGE complimented the endorsement of the Pan American Health Organisation (PAHO) Regional Immunization Action Plan by the PAHO Directing Council.

Le SAGE a félicité la Région des Amériques pour l'étape décisive qu'elle a franchie en éliminant la rubéole en août 2015 et s'est réjoui de l'interruption de la transmission de la rougeole au Brésil. Il a salué l'adoption du Plan d'action régional pour la vaccination par le Conseil directeur de l'Organisation panaméricaine de la Santé (OPS).

SAGE noted with concern that although there is some progress towards elimination, the high incidence of measles remains problematic in the Western Pacific Region, with large-scale outbreaks ongoing in China, Malaysia, the Philippines and Viet Nam.

Bien que des progrès aient été accomplis sur la voie de l'élimination, le SAGE a exprimé son inquiétude face à une incidence élevée de la rougeole qui reste problématique dans la Région du Pacifique occidental, avec des flambées de grande ampleur en cours en Chine, en Malaisie, aux Philippines au et Viet Nam.

SAGE complimented the Eastern Mediterranean Region for the adoption of its Eastern Mediterranean Vaccine Action Plan by the Regional Committee. Despite instability in several countries, good progress is being made in the Region, as exemplified by a national measles/rubella campaign in Yemen which achieved 91% coverage. Nevertheless, 3.2 million infants in 2014 did not receive DTP3, mainly due to the current geo-political situation. SAGE expressed grave concern that humanitarian emergencies remain a barrier to full immuniza-

Le SAGE a félicité la Région de la Méditerranée orientale pour l'adoption du Plan d'action de la Méditerranée orientale pour les vaccins par le Comité régional. Malgré les instabilités auxquelles elle est confrontée dans plusieurs pays, la région parvient à progresser, comme le montre par exemple une campagne nationale de lutte contre la rougeole/rubéole organisée au Yémen qui a atteint une couverture de 91%. Néanmoins, 3,2 millions de nourrissons n'ont pas reçu le DTC3 en 2014, essentiellement en raison de la situation géopolitique actuelle. Le SAGE s'est dit vivement préoccupé par la situation, notant

tion, and that vaccine stock-outs are a serious impediment to achieving high vaccination coverage.

In the South-East Asia Region, steady progress towards reaching the immunization goals was noted. Stakeholder engagement and the political commitment of India and other countries to strengthen immunization were well received. Positive developments were noted regarding the achievement of DTP3 coverage goals. A second dose of measles-containing vaccine (MCV) will be introduced in all countries by the end of 2015. Peer-learning between countries is fostered and all countries have established National Immunization Technical Advisory Groups (NITAGs).

In the European Region, political commitment on implementation of the European Vaccine Action Plan was observed. Progress on measles elimination was highlighted, with the lowest regional incidence since 2010, despite measles outbreaks in several countries. Nonetheless, susceptibility in age-groups ≥15 years is an ongoing problem. In addition to vaccine shortages, a new challenge is the immunization of arriving refugees, although, to date, no vaccine-preventable disease outbreaks have occurred in this population. The European Regional Office activities of the developing communication and advocacy tools on immunization were well received by countries.

Most unvaccinated infants in the world remain located in a few large under-performing countries. SAGE requested an in-depth analysis, expanded to the subnational level, to assess pockets of under-immunization, identify missed opportunities and assist with specifically targeting ongoing efforts. Data on missed opportunities for vaccination, when provided to countries, could enhance country commitment and implementation of local solutions.

SAGE expressed its concerns regarding private sector engagement in provision of routine immunization. Despite possible beneficial effects in some countries, this development poses a threat to routine immunization in others and may induce changes in the epidemiology of a particular disease if there is inadequate vaccine coverage, as in the case of varicella.

SAGE emphasized the need to advance work on refining guidance on the delivery of continuous immunization services during conflicts and other situations causing humanitarian crises.

SAGE applauded the development of the framework which outlines WHO's vision and mission for vaccines and immunization and called for its application in support of the GVAP goals. SAGE noted the critical need to continue to advocate for the inclusion of a vaccination target in the new sustainable development goals.[4]

[4] See https://sustainabledevelopment.un.org/?menu=1300; accessed November 2015.

que les urgences humanitaires demeurent un obstacle à la vaccination complète et que les ruptures de stocks de vaccins entravent sérieusement les efforts d'établissement d'une forte couverture vaccinale.

Le SAGE a signalé les progrès constants réalisés dans la Région de l'Asie du Sud-Est pour atteindre les objectifs de vaccination. Il a salué les efforts de mobilisation des parties prenantes et l'engagement politique de l'Inde et d'autres pays, et a constaté que les activités visant à atteindre les objectifs de couverture par le DTC3 ont évolué dans le bon sens. Une seconde dose du vaccin à valence rougeole (MCV) sera introduite dans tous les pays d'ici la fin 2015. L'échange des connaissances entre les pays est favorisé et tous les pays ont créé des groupes consultatifs techniques nationaux sur la vaccination.

Dans la Région européenne, le SAGE a constaté l'engagement politique manifesté en faveur de la mise en œuvre du Plan d'action européen pour les vaccins. Il a souligné les progrès réalisés en vue d'éliminer la rougeole, l'incidence régionale de la maladie ayant atteint son niveau le plus bas depuis 2010 malgré les flambées observées dans plusieurs pays. Toutefois, la sensibilité des tranches d'âge ≥15 ans est source de préoccupation récurrente. Outre la pénurie de vaccins, la vaccination des réfugiés arrivant dans la région constitue un nouveau défi, bien qu'aucune flambée de maladie évitable par la vaccination ne se soit déclarée à ce jour au sein de cette population. Les efforts déployés par le Bureau régional de l'Europe pour élaborer des outils de sensibilisation et de communication sur la vaccination ont été favorablement accueillis par les pays.

La majorité des nourrissons non vaccinés dans le monde se trouvent encore dans quelques grands pays aux résultats insuffisants. Le SAGE a demandé la réalisation d'une analyse approfondie, étendue au niveau infranational, pour étudier les poches de sous-vaccination, identifier les occasions manquées et fournir un appui ciblé aux efforts en cours. Lorsqu'elles sont communiquées aux pays, les données relatives aux occasions de vaccination manquées peuvent favoriser l'implication des pays et la mise en œuvre de solutions locales.

Le SAGE s'est dit préoccupé par la participation du secteur privé à la prestation des services de vaccination systématique. Bien que cette participation puisse être avantageuse dans certains pays, elle constitue une menace pour la vaccination systématique dans d'autres, risquant de changer l'épidémiologie d'une maladie donnée, comme c'est le cas pour la varicelle si la couverture vaccinale est inadéquate.

Le SAGE a souligné le besoin de continuer à affiner les orientations sur la poursuite des services de vaccination pendant les conflits aux conséquences humanitaires.

Le SAGE s'est félicité de l'établissement d'un cadre définissant la vision et la mission de l'OMS en matière de vaccination et a appelé à l'adaptation de ce cadre pour appuyer les objectifs du Plan d'action mondial pour les vaccins. Le SAGE a jugé indispensable de continuer à plaider en faveur de l'inclusion d'une cible relative à la vaccination dans les nouveaux objectifs de développement durable.[4]

[4] Voir https://sustainabledevelopment.un.org/?menu=1300 ; consulté en novembre 2015.

Report from the GAVI Alliance

The framework strategy of GAVI for 2016–2020 was approved by the GAVI Board in June 2015 and has 4 goals: (1) accelerate equitable uptake and coverage of vaccines; (2) increase effectiveness and efficiency of immunization delivery as an integrated part of strengthened health systems; (3) improve the sustainability of national immunization programmes; and (4) shape markets for vaccines and other immunization products.

Four key elements of the new GAVI strategy include: (a) more proactive and country-tailored grant management; (b) putting in place a new partners' engagement framework to provide targeted technical support to countries; (c) engagement in 6 strategic focus areas including supply chain, data, improving sustainability beyond co-financing, vaccine demand promotion, political will and leadership, management and coordination; and (d) differentiated approach focusing on 20 priority countries.

In December 2015, the GAVI Alliance Board will consider enhancing GAVI's engagement to bring the elimination of measles and rubella back on track with a funding support of up to US$ 800 million over the period 2016–2020.

GAVI continues to support the recovery of routine immunization and health systems in Ebola-affected countries. In addition, GAVI is committed to stockpile Ebola vaccine as soon as one is approved and licensed, and recommended by WHO.

Report of other advisory committees

1. The Global Advisory Committee on Vaccine Safety (GACVS) reported on its June 2015 meeting[5] and discussions that took place following this meeting on Ebola and malaria vaccines. Two issues were discussed: methodological improvements on the Vaccine Safety Net[6] (a network of websites assessed for credibility, content, accessibility and design), and generation of information sheets describing the observed rates of vaccine reactions. The safety profiles of important new vaccines against dengue, Ebola and malaria were also reviewed. Ebola and malaria vaccine reviews are presented in the corresponding sections of this report. For dengue vaccine, GACVS noted the higher risk of hospitalized dengue cases among vaccine recipients aged 2–5 years in the Asian study, while observing a consistent protective effect among vaccine recipients aged >9 years in Asian and Latin American studies. GACVS highlighted the importance of understanding factors associated with the increased hospitalization risk and to assess whether the protective effect among older age groups is sustained over time.

[5] See No. 29, 2015, pp. 365–372.

[6] See http://www.who.int/vaccine_safety/initiative/communication/network/vaccine_safety_websites/en/index3.html

Rapport de l'Alliance GAVI

Le cadre stratégique de l'Alliance GAVI pour la période 2016-2020, approuvé par le Conseil de l'Alliance GAVI en juin 2015, comporte 4 objectifs: 1) accélérer l'utilisation équitable des vaccins et améliorer la couverture vaccinale: 2) accroître l'efficacité et l'efficience des services de vaccination dans le cadre du renforcement des systèmes de santé: 3) améliorer la viabilité des programmes nationaux de vaccination: et 4) orienter le marché des vaccins et des autres produits vaccinaux.

Parmi les éléments clés de la nouvelle stratégie de l'Alliance GAVI figurent les 4 points suivants: a) une gestion des subventions plus proactive et mieux adaptée à chaque pays: b) l'établissement d'un nouveau cadre de l'engagement des partenaires pour fournir un appui technique ciblé aux pays: c) une intervention dans 6 domaines stratégiques, dont la chaîne d'approvisionnement, les données, la pérennité de l'action menée au-delà du cofinancement, la stimulation de la demande en vaccins, la direction et la volonté politiques, la gestion et la coordination: et d) une approche différenciée axée sur 20 pays prioritaires.

En décembre 2015, le Conseil de l'Alliance GAVI considérera le renforcement de l'action menée par l'Alliance pour relancer les efforts d'élimination de la rougeole et de la rubéole, avec un soutien financier atteignant US$ 800 millions sur la période 2016-2020.

L'Alliance GAVI continue d'apporter son appui au relèvement de la vaccination systématique et des systèmes de santé dans les pays touchés par Ebola. En outre, l'Alliance GAVI s'est engagée à soutenir la constitution d'un stock de vaccins contre Ebola dès qu'un vaccin aura été approuvé et homologué, et recommandé par l'OMS.

Rapports d'autres comités consultatifs

1. Le Comité consultatif mondial de la sécurité vaccinale (GACVS) a rendu compte de sa réunion de juin 2015[5] et des discussions sur le vaccin antipaludique et le vaccin contre Ebola qui ont suivi après discussion. Deux questions ont été abordées: l'amélioration de la méthodologie employée par le Réseau pour la sécurité des vaccins[6] (un réseau de sites web évalués sur la base de leur crédibilité, leur contenu, leur accessibilité et leur conception) et la production de fiches d'information indiquant les taux de réactions postvaccinales observés. Les profils d'innocuité de 3 nouveaux vaccins importants contre la dengue, Ebola et le paludisme ont également été examinés. Les conclusions relatives à Ebola et au paludisme sont présentées dans les sections du présent rapport consacrées à ces vaccins. Concernant le vaccin contre la dengue, le GACVS a constaté un risque accru d'hospitalisation pour la dengue parmi les sujets de 2 à 5 ans ayant reçu le vaccin dans l'étude asiatique, tandis qu'un effet protecteur était observé chez les sujets de >9 ans ayant reçu le vaccin dans les études menées en Asie et en Amérique latine. Le GACVS a souligné qu'il était important de comprendre les facteurs associés au risque accru d'hospitalisation et d'évaluer la persistance dans le temps de l'effet protecteur dans les tranches d'âge supérieures.

[5] Voir N° 29, 2015, pp. 365–372.

[6] Voir http://www.who.int/vaccine_safety/initiative/communication/network/vaccine_safety_websites/fr/

2. The Implementation Research Advisory Committee (IVIR-AC) discussed the following topics in June 2015:[7] research methods for community vaccine acceptance studies; non-specific effects of vaccines; polio vaccine modelling; the Global Vaccine Action Plan (GVAP) Decade of Vaccine Economics study; impact evaluation of hepatitis B vaccines; a pertussis impact modelling comparison study; a dengue vaccine modelling comparison exercise; and the development of guidance for the collection, assessment, and use of immunization data and analysis for Expanded Programme on Immunization (EPI) surveys.

SAGE requested that IVIR-AC (i) assess optimal immunization schedules based on both direct and indirect effects and not only direct effects, and (ii) explore research studies and methods including behavioural science studies for ranking the reasons behind lack of vaccine delivery and other "barriers to access".

3. The Immunization Practices Advisory Committee (IPAC) considered important programmatic issues at its October 2015 meeting including: plans to gather evidence and develop guidance on a 2nd year of life vaccination platform; new guidance on collecting, assessing and using immunization data; operational aspects of monitoring the switch to bivalent oral polio vaccine; and sustaining maternal and neonatal tetanus elimination. In addition, IPAC endorsed a proposal to streamline and harmonise country programme assessments. IPAC also endorsed the development of a new method for estimating vaccine wastage rates used in vaccine forecasting, incorporating improved calculation of opened-vial vaccine wastage rates. This new approach can help countries apply more realistic estimates of acceptable levels of wastage and improve service planning.

4. The Product Development for Vaccines Advisory Committee (PDVAC) in September 2015[8] reviewed a global vaccine pipeline analysis concerning 24 pathogens. The respiratory syncytial virus (RSV) vaccine pipeline continues to progress towards Phase 3 trials and a pathway for 3rd trimester maternal immunization pre-licensure trials has been agreed. Data indicating safety, immunogenicity, and placental transfer to infants are now available from clinical trials of a subunit RSV vaccine in pregnant women.

Group B streptococcus vaccine candidates are at an earlier development stage, but appear to be technically feasible, and fit within the growing maternal immunization agenda. PDVAC also noted the potential for Group A streptococcus, Norovirus, Enterotoxigenic *Escherichia coli*, Shigella, and Herpes simplex vaccines.

[7] See No. 37, 2015, pp. 477–484.

[8] See http://www.who.int/immunization/research/meetings_workshops/pdvac/en/; accessed October 2015.

2. Le Comité consultatif sur la vaccination et la recherche sur la mise en œuvre des vaccins (IVIR-AC) a abordé les questions suivantes en juin 2015:[7] méthodes de recherche pour étudier l'acceptation communautaire des vaccins; effets non spécifiques des vaccins; modélisation de la vaccination antipoliomyélitique; étude de la Décennie sur les effets économiques de la vaccination du GVAP; évaluation de l'impact des vaccins contre l'hépatite B; étude comparative de la modélisation de l'impact sur la coqueluche; exercice de comparaison des modèles sur les vaccins contre la dengue; et élaboration d'orientations sur la collecte, l'évaluation et l'utilisation des données de vaccination, ainsi que leur analyse pour les enquêtes du Programme élargi de vaccination.

Le SAGE a demandé au IVIR-AC i) d'évaluer les calendriers de vaccination optimaux en tenant compte des effets à la fois directs et indirects, et non seulement des effets directs, et ii) d'explorer les études et les méthodes de recherche, y compris dans le domaine des sciences comportementales, qui permettraient de classer les causes de la non distribution des vaccins, ainsi que les autres obstacles entravant l'accès à la vaccination.

3. Le Comité consultatif sur les pratiques vaccinales (IPAC) s'est penché sur d'importantes questions programmatiques lors de sa réunion d'octobre 2015 et notamment: la collecte de données et l'élaboration d'orientations relatives à une plateforme vaccinale pour la seconde année de vie: de nouvelles orientations sur la collecte, l'évaluation et l'utilisation des données de vaccination: et les aspects opérationnels du suivi de la transition vers le vaccin antipoliomyélitique oral bivalent et de l'élimination durable du tétanos maternel et néonatal. En outre, l'IPAC a approuvé une proposition visant à rationaliser et à harmoniser les évaluations des programmes de pays. Il a également donné son accord à la mise au point d'une nouvelle méthode d'estimation des taux de gaspillage des vaccins à des fins de prévision vaccinale, reposant sur un meilleur calcul du gaspillage des vaccins en flacons ouverts. Cette nouvelle approche devrait permettre aux pays d'adopter des estimations plus réalistes des taux acceptables de gaspillage et de mieux planifier leurs services.

4. Le Comité consultatif sur le développement de produits pour les vaccins (PDVAC) a examiné en septembre 2015[8] les résultats d'une analyse mondiale des vaccins en cours de développement contre 24 agents pathogènes. Le développement des vaccins contre le virus respiratoire syncytial (VRS) continue de progresser en vue des essais de phase 3 et il a été convenu d'une marche à suivre pour la conduite d'essais préhomologation de vaccination maternelle lors du 3e trimestre de grossesse. On dispose désormais de données d'innocuité, d'immunogénicité et de transfert placentaire provenant d'essais cliniques sur l'utilisation d'un vaccin sous-unité contre le VRS chez les femmes enceintes.

Les vaccins candidats contre les streptocoques du groupe B en sont à un stade moins avancé de développement, mais semblent réalisables sur le plan technique et s'intègrent bien dans un programme de vaccination maternelle de plus en plus complet. Le PDVAC a également mentionné les possibilités de développement de vaccins contre les streptocoques du groupe A, les norovirus, *Escherichia coli* entérotoxinogène, Shigella et le virus de l'herpès simplex.

[7] Voir N° 37, 2015, pp. 477–484.

[8] Voir http://www.who.int/immunization/research/meetings_workshops/pdvac/en/: consulté en octobre 2015.

PDVAC noted the initiation of WHO's Blueprint for Emergency Research & Development Preparedness and Research Response, and recognised that emerging pathogens need to be included in the annual PDVAC pipeline analyses. The availability of specific data for decision-making on transition from pre-clinical to Phase 1 trials was also an area that PDVAC should consider.

5. The Expert Committee on Biological Standardization (ECBS) in October 2015 adopted: revised WHO guidelines on good manufacturing practices for biological products; new guidelines on stability evaluation of vaccines for use under extended controlled temperature conditions; and revised recommendations to assure the quality, safety and efficacy of recombinant human papilloma virus-like particle vaccines.

ECBS also established for the first time WHO reference preparations for Ebola virus. These reagents will allow comparison of data and outcomes from clinical trials across different studies.

Polio eradication

SAGE reviewed all readiness criteria for the global withdrawal of type 2 oral poliovirus vaccine (OPV2) as well as type 2 vaccine-derived poliovirus (VDPV2) epidemiology, in order to assess whether to confirm April 2016 as the date for the globally coordinated withdrawal of OPV2 by switching from use of trivalent OPV (tOPV) to bivalent OPV (bOPV).

Since August 2014, no wild poliovirus has been detected in any country except type 1 in Afghanistan and Pakistan. The Global Commission for the Certification of Poliomyelitis Eradication has certified that wild poliovirus type 2 has been eradicated worldwide. The most recent case of poliomyelitis due to wild poliovirus type 3 was detected in November 2012. SAGE congratulated the Global Polio Eradication Initiative (GPEI) and Member States on this important progress.

Since the beginning of 2014, persistent circulating VDPV2 (cVDPV2) has been detected only in Nigeria and Pakistan. Both countries have substantially improved type 2 population immunity, through increased frequency and quality of tOPV campaigns, supplemented by inactivated poliovirus vaccine (IPV). As a result, both countries have interrupted transmission of highly mutated cVDPV2 strains that had established prolonged circulation, and have likely stopped transmission of new persistent cVDPV2 strains that emerged in 2014–2015. The GPEI has optimized its strategy to prevent emergence of VDPV2 through an extensive set of tOPV campaigns, more sensitive definitions of cVDPV2, immediate response to any VDPV2 detection and updated its guidelines[9] for responding to any cVDPV outbreak.

Le PDVAC a pris note de la mise en application du Plan OMS de préparation des activités de recherche et de développement pour les situations d'urgence et de riposte en matière de recherche, et a convenu de la nécessité d'inclure les pathogènes émergents dans les analyses annuelles du PDVAC sur les produits en cours de développement. Le PDVAC devrait également tenir compte de la disponibilité de données spécifiques permettant de décider de l'opportunité de la transition de la phase préclinique aux essais cliniques phase 1.

5. Le Comité d'experts de la standardisation biologique (ECBS) a adopté en octobre 2015 les lignes directrices révisées de l'OMS sur les bonnes pratiques de fabrication des produits biologiques, de nouvelles lignes directrices sur l'évaluation de la stabilité des vaccins à utiliser dans des conditions étendues de température contrôlée, et des recommandations révisées pour garantir la qualité, l'innocuité et l'efficacité des vaccins recombinants à pseudoparticules virales du papillome humain.

L'ECBS a également établi les toutes premières préparations de référence pour le virus Ebola. Ces réactifs permettront une comparaison des données et des résultats de différents essais cliniques.

Éradication de la poliomyélite

Le SAGE a examiné tous les critères relatifs à l'état de préparation au retrait mondial du vaccin antipoliomyélitique oral de type 2 (VPO2), ainsi que l'épidémiologie du poliovirus dérivé d'une souche vaccinale de type 2 (PVDV2), afin d'évaluer s'il fallait confirmer ou non le retrait coordonné du VPO2 à l'échelle mondiale en avril 2016, le VPO trivalent (VPOt) étant dès lors remplacé par le VPO bivalent (VPOb).

Depuis août 2014, aucun poliovirus sauvage n'a été détecté dans le monde, à l'exception du virus de type 1 observé en Afghanistan et au Pakistan. La Commission mondiale de certification de l'éradication de la poliomyélite a certifié que le poliovirus sauvage de type 2 avait été éradiqué dans le monde entier. Le cas le plus récent de poliomyélite dû à poliovirus sauvage de type 3 a été détecté en novembre 2012. Le SAGE a félicité l'Initiative mondiale pour l'éradication de la poliomyélite (IMEP) et les États Membres pour ces progrès remarquables.

Depuis le début de l'année 2014, seuls le Nigéria et le Pakistan ont dépisté une transmission persistante de PVDV2 circulants (PVDVc2). Ces pays sont tous deux parvenus à renforcer notablement l'immunité de la population au virus de type 2 grâce à des campagnes plus fréquentes et de meilleure qualité d'administration du VPOt, assorti du vaccin antipoliomyélitique inactivé (VPI). Par conséquent, les 2 pays ont réussi à interrompre la transmission des souches PVDVc2 fortement mutées qui circulaient de longue date et ont probablement mis fin à la transmission de nouvelles souches persistantes de PVDVc2 apparues en 2014-2015. L'IMEP a optimisé sa stratégie de prévention pour éviter toute émergence de PVDV2, prévoyant une série complète de campagnes d'administration du VPOt, une définition plus sensible des PVDVc2, une riposte immédiate à toute détection de PVDV2 et l'actualisation de ses lignes directrices[9] relatives aux activités de riposte en cas de flambée de PVDVc.

[9] See http://www.polioeradication.org/Portals/0/Document/Resources/VDPV_ReportingClassification.pdf

[9] Voir http://www.polioeradication.org/Portals/0/Document/Resources/VDPV_ReportingClassification.pdf

SAGE reviewed progress against the established criteria to confirm readiness for OPV2 withdrawal, and concluded that these criteria have largely been met, and highlighted areas requiring further risk mitigation measures.

SAGE noted a recent reduction in supply that may delay IPV introduction until after the switch from tOPV to bOPV in up to 28 tier 3 and 4 countries. SAGE affirmed that the switch should proceed since IPV has only a limited role in preventing VDPV2 emergence. IPV's primary value is in minimising the occurrence of paralytic disease from any VDPV2 outbreak after the switch. This value will increase with time after the switch, as birth cohorts that have not received OPV2 increase. The risk of VDPV2 emergence is being reduced principally by an extensive series of tOPV supplementary immunization activities (SIAs) in 43 countries in the months before the switch. In addition to tOPV campaigns, all highest risk (tier 1 and 2) countries except Indonesia will introduce IPV before the switch. The countries affected by the delay are at lower risk (tier 3 and 4). Population immunity against type 2 is high in these countries due to consistently high routine vaccination coverage which minimizes the risk of VDPV2 emergence and spread. It is anticipated that all countries will receive IPV supplies within approximately 3 months of the switch. Catch-up vaccination will be conducted when sufficient supplies are available. Stocks of mOPV2 and IPV are available for outbreak response if VDPV2 is detected in any country.

SAGE concluded that the public health risks associated with the continued use of the type 2 component contained in tOPV far outweigh the risk of new VDPV2 emergence after use of OPV2 is stopped, even in countries where IPV introduction will be delayed.

SAGE reaffirmed that the withdrawal of OPV2 should proceed in April 2016. This date is now definitively confirmed. Every country should stop using tOPV on a single day of its choice between 17 April and 1 May 2016, and remove all stocks of tOPV from service delivery points within 2 weeks of that day, and confirm their removal to WHO.

SAGE emphasised that withdrawal of OPV2 can never be entirely risk-free, and strong implementation of risk-mitigation measures is crucial. SAGE advised Pakistan to implement its revised schedule of sSIAs to ensure that the mix of tOPV and bOPV used during the SIAs and their geographic scope will provide sufficient population immunity against type 2 polio before the switch. SAGE advised the GPEI to ensure a full outbreak response to interrupt the cVDPV2 outbreaks in Guinea and in South Sudan within 120 days of outbreak confirmation.

SAGE emphasised that all countries must ensure regulatory approval of bOPV for routine immunization before April 2016 and that the UNICEF Supply Division, PAHO

Le SAGE a examiné les progrès accomplis par rapport aux critères fixés pour confirmer que l'on est prêt au retrait du VPO2 et a conclu que ces critères avaient été en grande partie satisfaits et a mis en exergue les domaines où des mesures supplémentaires de réduction des risques sont nécessaires.

Le SAGE a constaté que dans près de 28 pays de niveaux 3 et 4, une récente baisse de l'approvisionnement pourrait retarder l'introduction de VPI, de sorte qu'elle n'interviendrait qu'après la transition du VPOt au VPOb. Le SAGE a affirmé que la transition doit toutefois avoir lieu car le VPI n'a qu'un rôle limité dans la prévention de l'émergence de PVDV2. L'intérêt principal du VPI est qu'il permet de réduire les risques de maladie paralytique résultant d'une flambée de PVDV2 après la transition. Son utilité deviendra de plus en plus grande après la transition, au fur et à mesure que grandissent les cohortes de naissance qui n'ont pas reçu le VPO2. La principale mesure permettant de réduire le risque d'émergence de PVDV2 consiste en l'adoption, dans 43 pays, d'une série complète d'activités de vaccination supplémentaire (AVS) avec le VPOt dans les mois précédant la transition. Outre les campagnes d'administration de VPOt, tous les pays les plus à risque (niveaux 1 et 2), à l'exception de l'Indonésie, procèderont à l'introduction du VPI avant la transition. Les pays concernés par le retard d'introduction du VPI présentent un risque moindre (niveaux 3 et 4). La population de ces pays possède une forte immunité contre le virus de type 2, ayant généralement bénéficié d'une bonne couverture de la vaccination systématique: ainsi, le risque d'émergence et de propagation du PVDV2 y est minime. Il est prévu que tous les pays soient approvisionnés en VPI dans un délai d'environ 3 mois après la transition. Une vaccination de rattrapage sera effectuée lorsque l'approvisionnement sera suffisant. Des stocks de VPOm2 et de VPI sont disponibles pour riposter aux flambées en cas de détection de PVDV2 dans un pays quelconque.

Le SAGE a conclu que les risques de santé publique associés à l'utilisation persistante de la composante de type 2 contenue dans le VPOt sont bien supérieurs au risque d'une nouvelle émergence de PVDV2 après l'arrêt du VPO2, même dans les pays où l'introduction du VPI sera retardée.

Le SAGE a réaffirmé que le retrait du VPO2 devait avoir lieu en avril 2016. Cette date est à présent définitivement confirmée. Tous les pays doivent cesser d'administrer le VPOt à une date précise de leur choix, comprise entre le 17 avril et le 1er mai 2016, puis retirer tous les stocks de VPOt des lieux de prestation de services dans les 2 semaines qui suivent cette date, et enfin confirmer le retrait à l'OMS.

Le SAGE a souligné que le retrait du VPO2 ne peut être entièrement dénué de risques et que la pleine mise en œuvre des mesures de réduction des risques est essentielle. Le SAGE a invité le Pakistan à suivre le calendrier révisé d'AVS pour veiller à ce que les proportions respectives de VPOt et de VPOb administrés durant les AVS, ainsi que la portée géographique des AVS, entraînent une immunité suffisante de la population contre le poliovirus de type 2 avant la transition. Le SAGE a conseillé à l'IMEP de mener une riposte complète contre la flambée de PVDVc2 en Guinée et au Soudan du Sud pour parvenir à l'interrompre dans les 120 jours suivant la confirmation.

Le SAGE a souligné que tous les pays doivent homologuer le VPOb aux fins de la vaccination systématique avant avril 2016 et que la Division des approvisionnements de l'UNICEF,

Revolving Fund and WHO should secure the global supply of prequalified bOPV.

SAGE advised GPEI to accelerate implementation of the WHO Global Action Plan for containment (GAPIII) including: (i) all countries completing phase I; (ii) regional focal points closely monitoring country activities and ensuring that each country completes its inventories of facilities that hold or handle polioviruses, and destroys or commits to destroying WPV2 by end 2015 and any other type 2 containing materials including Sabin poliovirus by July 2016.

SAGE advised GPEI to develop a targeted advocacy and communication plan to engage key countries and stakeholders to ensure completion of phase I and implementation of phase II, including establishment of a national containment authority and national regulation for containment of poliovirus in designated essential poliovirus facilities.

Following recent shortfalls in IPV supply, SAGE advised the GPEI to communicate clearly with countries on the rationale for proceeding with the tOPV to bOPV switch and emphasized that even in the event of further changes in IPV supply, the switch date will not be changed. SAGE requested its Polio Working Group to provide urgent guidance on optimal management of IPV supply and mitigation of other risks in case the IPV supply is further reduced. SAGE endorsed the GPEI's approach to prioritization of IPV use, to be applied if the IPV supply is reduced further, as follows: first ensuring introduction in tier 1 and 2 countries before the switch; making stocks available for outbreak response after the switch; minimizing delays in introduction, stock-outs, and the number of countries affected.

SAGE also received an update on polio legacy planning. SAGE acknowledged progress being made, underscored the importance of this work, and encouraged further engagement of WHO regional offices to ensure adequate technical support to countries.

Ebola vaccines and vaccination

SAGE reviewed: available information on epidemiology, risk factors and transmission patterns of Ebola virus disease (EVD); the status of vaccine development; preliminary results from the most advanced vaccine candidates; preparations for vaccine deployment; and projections of the impact of vaccination in different epidemiological scenarios.

The accelerated development of several candidate vaccines is unprecedented and a testament to the value of partnership, participatory approaches and coordination. The lessons learnt from this experience are being leveraged to develop a blueprint for research preparedness and rapid research response for future epidemics due to other microbes.

le Fonds renouvelable de l'OPS et l'OMS doivent garantir un approvisionnement mondial suffisant de VPOb préselectionné.

Le SAGE a invité l'IMEP à accélérer la mise en œuvre du Plan d'action mondial de l'OMS pour le confinement des poliovirus (GAPIII), visant notamment: i) l'achèvement de la phase I par tous les pays: ii) le suivi des activités des pays par les centres de liaison régionaux pour vérifier que chaque pays établit l'inventaire complet des établissements détenant ou manipulant des poliovirus et détruit, ou s'engage à détruire, les stocks de PVS2 d'ici la fin 2015, ainsi que tout autre produit contenant un virus de type 2, y compris le poliovirus Sabin, d'ici juillet 2016.

Le SAGE a conseillé à l'IMEP d'élaborer un plan ciblé de sensibilisation et de communication afin de faciliter le dialogue avec les principaux pays et partenaires et parvenir à l'achèvement de la phase I et la mise en œuvre de la phase II, notamment la création d'une autorité nationale de confinement et l'établissement d'une réglementation nationale relative au confinement des poliovirus dans les établissements essentiels désignés.

Compte tenu de la pénurie récente de VPI, le SAGE a invité l'IMEP à expliquer clairement aux pays pourquoi la transition du VPOt au VPOb aura lieu comme prévu et a souligné que même si l'approvisionnement de VPI devait de nouveau évoluer, la date fixée pour la transition ne serait pas modifiée. Le SAGE a demandé à son groupe de travail sur la poliomyélite d'élaborer de toute urgence des orientations sur la gestion optimale des stocks de VPI et la réduction des autres risques en cas de nouvelle baisse de l'approvisionnement en VPI. Le SAGE a approuvé l'approche proposée par l'IMEP pour établir les priorités en matière d'utilisation du VPI si l'approvisionnement diminuait de nouveau, à savoir: assurer en premier lieu l'introduction du VPI dans les pays de niveaux 1 et 2 avant la transition: allouer des stocks aux activités de riposte aux flambées après la transition: réduire au minimum les introductions tardives, les ruptures de stock et le nombre de pays concernés.

Le SAGE a également pris connaissance des dernières évolutions en matière de planification de la transmission des acquis. Il a pris note des progrès réalisés, souligné l'importance de ces travaux et encouragé une plus grande participation des bureaux régionaux de l'OMS afin que les pays bénéficient d'un soutien technique adéquat.

Vaccins et vaccination contre le virus Ebola

Le SAGE a examiné les dernières informations concernant l'épidémiologie, les facteurs de risque et les caractéristiques de transmission de la maladie à virus Ebola: l'état d'avancement des activités de mise au point de vaccins: les résultats préliminaires obtenus pour les vaccins candidats les plus avancés: la préparation au déploiement des vaccins: et les projections quant à l'impact de la vaccination selon différents scénarios épidémiologiques.

Ebola a fait l'objet d'un développement accéléré de plusieurs vaccins candidats, réalisation sans précédent qui témoigne du mérite des approches fondées sur les partenariats, la participation et la coordination. Les enseignements tirés de cette expérience servent désormais à élaborer un plan de préparation des activités de recherche et de riposte en matière de recherche pour combattre les futures épidémies occasionnées par d'autres micro-organismes.

The 4 leading vaccine candidates[10] are immunogenic in a 1-dose or 2-dose schedule. Interim results from a Phase 3 trial suggest that rVSV-ΔG-ZEBOV is efficacious, safe, and likely to be effective at the population level when delivered during an EVD outbreak, using a ring vaccination strategy.

Available safety data for both ChAd3-ZEBOV and rVSV-ΔG-ZEBOV vaccines indicate an acceptable safety profile in healthy adults. Data on safety in children, pregnant women, and those with underlying medical conditions are insufficient to draw conclusions.

Based on available data SAGE concluded that vaccination is likely to provide added value in controlling outbreaks of EVD caused by *Zaire ebolavirus* (ZEBOV) species. Currently, there are no data to support any recommendations on vaccines against other species of *ebolavirus*. However, one leading candidate vaccine has a multivalent "boost" component and a bivalent ChAd3-vectored *Zaire-Sudan ebolavirus* vaccine is under development.

SAGE noted that candidate vaccines are currently only being used in the context of clinical trials, or in exceptional circumstances in countries where no trial is ongoing in order to respond to a new confirmed EVD case, within the context of expanded use of an investigational vaccine. Recommendations for use as an additional public health tool will depend on the vaccines receiving regulatory approval (i.e. full licensure, conditional licensure, or emergency use authorization outside a clinical trial setting).

In light of the emerging data on the persistence of Ebola virus in survivors of EVD and transmission of infection to sexual contacts, SAGE also noted that the expanded use of vaccines in contacts of survivors is under consideration, within the context of expanded use of an investigational vaccine as part of a study.

Based on review of current data SAGE made the following provisional recommendations, which are not vaccine-specific and will be reviewed and revised in light of the emerging data from different Ebola vaccines:

- Vaccination during outbreaks should be part of an integrated strategy and complement other public health measures to interrupt transmission. It does not substitute for full-time personal protective equipment use, contact tracing and other infection control measures.
- The main objectives for vaccination are interruption of transmission and individual protection for those at high risk for infection during an outbreak.

[10] See http://www.who.int/immunization/sage/meetings/2015/october/2_WHO_SAGE_WG_ebola_vaccines_and_immunization_MPP_VM_AMHR.pdf?ua=1

Les 4 principaux vaccins candidats[10] sont immunogènes après l'administration d'1 ou 2 doses. Les résultats préliminaires d'un essai de phase 3 semblent confirmer l'innocuité et l'efficacité du vaccin rVSV-ΔG-ZEBOV, indiquant qu'il est probablement efficace à l'échelle de la population lorsqu'il est administré selon une stratégie de «vaccination en ceinture» durant une flambée de maladie à virus Ebola.

Les données d'innocuité disponibles pour les vaccins ChAd3-ZEBOV et rVSV-ΔG-ZEBOV indiquent qu'ils ont tous deux un profil d'innocuité acceptable chez les adultes en bonne santé. On ne dispose pas de données suffisantes pour formuler des conclusions quant à l'innocuité de ces vaccins chez l'enfant, la femme enceinte et les personnes présentant une affection sous-jacente.

Sur la base des données disponibles, le SAGE a conclu que la vaccination apportera probablement une valeur ajoutée aux efforts de lutte contre les flambées de maladie à virus Ebola dues à l'espèce *ebolavirus Zaïre* (ZEBOV). À ce jour, on ne dispose pas des données nécessaires pour émettre quelque recommandation que ce soit concernant les vaccins contre d'autres espèces de virus Ebola. Cependant, l'un des principaux vaccins candidats présente une composante de «rappel» multivalente et un vaccin bivalent *Zaïre-Soudan* à vecteur ChAd3 est en cours d'élaboration.

Le SAGE a noté que les vaccins candidats sont actuellement utilisés uniquement dans le cadre d'essais cliniques, ou, dans des circonstances exceptionnelles dans les pays où aucun essai n'est en cours, afin de réagir à un nouveau cas confirmé de maladie à virus Ebola, mais à titre d'utilisation étendue d'un vaccin expérimental. L'utilisation de ces vaccins en tant qu'instrument supplémentaire de santé publique ne pourra être recommandée que lorsqu'ils auront été approuvés par les autorités réglementaires (homologation complète, homologation conditionnelle ou autorisation d'utilisation en situation d'urgence en dehors du cadre des essais cliniques).

Au vu de nouvelles données portant sur la persistance du virus chez les survivants de la maladie à virus Ebola et sur la transmission de l'infection aux contacts sexuels, le SAGE a également noté qu'une utilisation étendue des vaccins chez les sujets en contact avec des survivants est envisagée, strictement à titre d'utilisation étendue d'un vaccin expérimental dans le cadre d'une étude.

Après examen des données actuelles, le SAGE a émis les recommandations provisoires suivantes, qui sont applicables à tous les vaccins. Elles seront réévaluées et révisées à la lumière des nouvelles données obtenues concernant les différents vaccins contre le virus Ebola:

- La vaccination en cours de flambée doit faire partie d'une stratégie de riposte intégrée et s'inscrire en complément d'autres mesures de santé publique visant à interrompre la transmission. Elle ne saurait se substituer à l'utilisation des équipements de protection individuelle, aux activités de recherche des contacts et aux autres mesures de lutte contre l'infection.
- Les principaux objectifs de la vaccination consistent à interrompre la transmission et à assurer la protection individuelle des personnes à haut risque d'infection durant une flambée.

[10] Voir http://www.who.int/immunization/sage/meetings/2015/october/2_WHO_SAGE_WG_ebola_vaccines_and_immunization_MPP_VM_AMHR.pdf?ua=1

- Health-care workers, as well as certain other categories of individuals with high likelihood of exposure to infectious body fluids, including informal health-care providers and those involved in funeral rites, are at higher risk for infection than the general population. The categories of front-line workers and other risk groups may vary between communities and should be defined locally.
- The vaccination delivery strategy will depend on the extent of the spread of disease, disease incidence at the time when vaccination is initiated, status of implementation of other control measures, effectiveness of contact tracing, and available supply of vaccine. Regular reviews of the epidemiological data should inform adjustments to the delivery strategies throughout the outbreak. Potential strategies include ring vaccination, geographic targeting of an area (mass vaccination) and vaccination of front-line workers. When more data are available, more precise recommendations on the choice of vaccination strategy will be considered.

SAGE proposed the following issues be taken into consideration:

- Pregnant women and infants have very high case fatality rates and may benefit from the indirect effects of their close contacts being vaccinated.
- Careful planning should ensure readiness for vaccine introduction as soon as feasible. The work of the Global Ebola Vaccine Implementation Team to develop tools and generic deployment plans should be completed.

SAGE made the following recommendations for additional data review or research:

- Researchers should share data from pregnant women who were inadvertently vaccinated, and from HIV-positive subjects if included in the ongoing trials. Future trials should consider collecting data from children, adolescents, pregnant and lactating women, and immunocompromised individuals.
- Efforts to develop vaccines against filoviruses other than ZEBOV, such as Sudan, Bundibugyo and Marburg should be pursued. Multivalent filovirus vaccines are desirable.
- Should data on safety, immunogenicity or efficacy preclude the vaccination of pregnant women, alternate preventive strategies should be evaluated, recognizing the high case fatality rate in this group.
- All trials should carefully document adverse events using standard definitions, including duration, severity and sequelae. In particular, for rVSV-ΔG-ZEBOV vaccine, safety monitoring should document and clearly distinguish arthritis from arthralgia.

- Les agents de santé, ainsi que certaines autres catégories de personnes susceptibles d'être exposées à des liquides biologiques infectieux, y compris les prestataires informels de soins de santé et les sujets participant aux rites funéraires, présentent un risque d'infection plus élevé que la population générale. Ces catégories d'agents de première ligne et d'autres groupes à risque peuvent varier d'une communauté à l'autre et doivent être définis localement.
- La stratégie de vaccination dépendra du degré de propagation de la maladie, de son incidence au moment où la vaccination commence, de la mise en œuvre des autres mesures de lutte contre l'infection, de l'efficacité de la recherche des contacts et des stocks de vaccin disponibles. Les données épidémiologiques seront régulièrement examinées pour décider des modifications à apporter aux stratégies de vaccination tout au long de la flambée. Parmi les stratégies possibles figurent la vaccination en ceinture, le ciblage d'une zone géographique déterminée (vaccination de masse) et la vaccination des agents de première ligne. Lorsque de nouvelles données seront disponibles, des recommandations plus précises sur le choix de la stratégie de vaccination pourront être envisagées.

Le SAGE a proposé que les points suivants soient pris en compte:

- Les femmes enceintes et les nourrissons, qui présentent un taux de létalité très élevé, pourraient bénéficier des effets indirects d'une vaccination de leurs contacts proches.
- Une planification minutieuse s'impose pour assurer un état de préparation adéquat à l'introduction des vaccins dès que cela sera possible. L'Équipe mondiale de mise en œuvre de la vaccination contre Ebola, chargée de mettre au point des outils et des plans généraux de déploiement, doit mener ses travaux à bon terme.

Le SAGE a formulé les recommandations suivantes concernant l'étude des données supplémentaires et les activités de recherche:

- Les chercheurs devraient partager les données relatives aux femmes enceintes vaccinées par inadvertance, ainsi qu'aux sujets positifs pour le VIH, s'ils ont été inclus dans des essais en cours. Dans le cadre des essais futurs, on s'efforcera de recueillir des données concernant les enfants, les adolescents, les femmes enceintes ou allaitantes et les sujets immunodéprimés.
- Il convient de poursuivre les efforts de développement de vaccins contre les filovirus autres que ZEBOV, notamment les virus Soudan, Bundibugyo et Marburg. Il serait particulièrement intéressant d'obtenir des vaccins multivalents contre les filovirus.
- Si les données sur l'innocuité, l'immunogénicité ou l'efficacité des vaccins devaient imposer une exclusion des femmes enceintes de la vaccination, d'autres stratégies de prévention devraient être examinées, compte tenu du taux élevé de létalité dans cette population.
- Dans tous les essais cliniques, les manifestations indésirables devront être soigneusement consignées à l'aide de définitions normalisées, notamment pour indiquer leur durée, leur gravité et leurs séquelles. En particulier, s'agissant du vaccin rVSV-ΔG-ZEBOV, la surveillance de l'innocuité vaccinale doit relever et clairement distinguer les manifestations d'arthrite et d'arthralgie.

- Evaluation or modeling of the long-term duration of protection for all candidate vaccines should be carried out.
- The feasibility and effectiveness of different delivery strategies and interventions to improve community acceptance should be evaluated.

- Community-based participatory approaches to engage participants in all stages of clinical trials, including design, monitoring and evaluation, should be implemented.
- Vaccine thermostability should be optimized to meet WHO criteria for programmatic suitability for prequalification.
- Ongoing efforts to model the impact of different Ebola vaccination strategies should be continued and expanded to further inform their respective value in controlling an outbreak.

- Pre-approved and pre-positioned protocols and local research capacity strengthening in countries at risk for outbreaks should be put in place to facilitate rapid implementation of relevant studies, including assessment of newer vaccine products, as outlined in the blueprint for research during public health emergencies being developed under the leadership of WHO.

Measles and rubella

Annually >1 million measles-related deaths are prevented globally through measles vaccination. However, outbreaks of measles continue to occur and progress towards global control targets and regional elimination goals have plateaued. SAGE reaffirmed its previous assessment that the 2015 global measles control milestones as well as regional measles and rubella elimination goals are off-track (except in the Americas). SAGE supported the conduct of a midterm review of the global measles and rubella strategic plan to better understand why targets are being missed and propose measures to accelerate progress.

Recent outbreaks of measles in countries achieving high level control, or near elimination, have had a bimodal age distribution, involving infants below the recommended age for vaccination, and adolescents and young adults.

Infants of mothers with vaccine-induced immunity lose passive immunity to measles approximately 3 months earlier than infants of mothers with immunity acquired via measles disease. A systematic review found that MCV given from 6 months of age is immunogenic, effective and safe. Vaccine effectiveness increases with the infant's age at vaccination. Some evidence of a blunted response to MCV2 after MCV1 in infants aged <9 months was found with respect to geometric mean titres and avidity, but not for the proportion seropositive or for cellular immunity.

- La durée à long terme de la protection conférée par tous les vaccins candidats doit être évaluée ou modélisée.

- La faisabilité et l'efficacité des différentes interventions et stratégies de vaccination doivent être évaluées pour veiller à une meilleure acceptation de la vaccination par les communautés.
- Une approche communautaire participative doit être adoptée pour favoriser la participation de la communauté à toutes les étapes des essais cliniques, y compris au stade de la conception, du suivi et de l'évaluation.
- La thermostabilité des vaccins doit être optimisée pour satisfaire aux critères de l'OMS concernant l'adéquation programmatique des vaccins en vue de leur préqualification.
- Il convient de poursuivre et d'intensifier les efforts déjà engagés pour modéliser l'impact de différentes stratégies de vaccination contre Ebola, ce qui permettra d'évaluer l'intérêt de chacune de ces stratégies dans la lutte contre les flambées.
- Dans les pays à risque de flambées, il importe de mettre en place des protocoles préapprouvés et prépositionnés, ainsi que des mesures de renforcement du potentiel de recherche local, pour faciliter la conduite rapide d'études pertinentes, notamment l'évaluation des nouveaux produits vaccinaux, comme le prévoit le plan sur les travaux de recherche lors des urgences de santé publique qui est en cours d'élaboration sous la direction de l'OMS.

Rougeole et rubéole

Chaque année, la vaccination antirougeoleuse permet d'éviter plus d'un million de décès liés à la rougeole à l'échelle mondiale. Néanmoins, des flambées de rougeole continuent de se déclarer et les progrès vers les cibles mondiales dans la lutte contre cette maladie et les objectifs régionaux d'élimination ont atteint un plateau. Le SAGE a réaffirmé sa précédente évaluation selon laquelle les étapes mondiales de 2015 dans la lutte contre la rougeole ainsi que les objectifs régionaux en matière d'élimination de la rougeole et de la rubéole ne pouvaient être atteints dans les temps (sauf dans les Amériques). Il a appuyé la réalisation d'un examen à mi-parcours du plan stratégique mondial de lutte contre la rougeole et la rubéole afin de mieux comprendre pourquoi les cibles restaient hors d'atteinte et proposer des mesures pour accélérer les progrès.

Les récentes flambées de rougeole intervenues dans des pays parvenant à un grand niveau de contrôle de cette maladie ou proches de l'élimination on fait apparaître une distribution bimodale en fonction de l'âge, incluant des enfants plus jeunes que l'âge recommandé pour la vaccination, et des adolescents et des jeunes adultes.

Les nourrissons nés de mères possédant une immunité induite par la vaccination perdent leur immunité passive à l'égard de la rougeole approximativement 3 mois plus tôt que les enfants nés de mères immunisées après avoir contracté la maladie. Une revue systématique a constaté que l'administration du MCV à partir de 6 mois était immunogène, efficace et sans risque. L'efficacité vaccinale augmente avec l'âge de l'enfant lors de la vaccination et on a relevé certains éléments indiquant une réponse atténuée au vaccin MCV2 après l'administration du MCV1 avant 9 mois d'après les moyennes géométriques des titres en anticorps et l'avidité, mais pas pour ce qui concerne le pourcentage de séropositifs ou l'immunité cellulaire.

SAGE concluded that the available evidence supports use of MCV before 9 months of age and recommends that infants from 6 months of age receive a dose of measles containing vaccine in the following circumstances: (1) during a measles outbreak as part of intensified service delivery; (2) during SIAs in settings where risk of measles among infants remains high (e.g. in endemic countries experiencing regular outbreaks); (3) for internally displaced populations and refugees, and populations in conflict zones; (4) for individual children at high risk of contracting measles (e.g. contacts of known measles cases or in settings with increased risk of exposure during outbreaks such as day-care facilities); (5) for infants travelling to countries experiencing measles outbreaks; and (6) for infants known to be HIV-positive (see 2009 measles vaccine position paper).[11]

Because immunogenicity and effectiveness are lower than for doses administered at a later age and concern about the long-term effectiveness of an early 2-dose schedule, MCV administered before the age of 9 months should be considered a supplementary dose and recorded on the child's vaccination record as "MCV0". Children who receive a MCV0 dose should then receive subsequent measles-containing vaccines at the recommended ages according to the national schedule.

Available evidence on safety and immunogenicity of rubella and mumps-containing vaccines support their use from 6 months of age. Countries using measles-rubella (MR) or measles, mumps and rubella (MMR) in their national schedule should use the combined vaccine rather than measles-only formulations in children aged <1 year. SAGE recognizes that this is an off-label use and recommends that national programmes do not restrict the use of the vaccine in the <1 year age group. SAGE recommended further clinical, immunological, epidemiological and modelling studies regarding the impact of different measles vaccination schedules.

The multi-country analysis of the impact of SIA strategies and comparison of surveillance and susceptibility data are still at an early stage. Mathematical modeling suggests a high quality measles SIA (reaching >90% of susceptible children) targeting children aged <5 years is equally effective and more cost-efficient than a lower quality wider age range SIA (e.g. targeting children aged <10 years reaching >70% of susceptible children). An introductory MR SIA algorithm to guide countries on which age groups to target appears promising. Further work is needed to confirm applicability and allow an integrated measles-rubella approach.

[11] See No. 35, 2009, pp. 349–360.

Le SAGE a conclu que les éléments disponibles étaient en faveur de l'utilisation du MCV avant 9 mois et recommande que les nourrissons à partir de 6 mois reçoivent une dose de vaccin à valence rougeole dans les circonstances suivantes: 1) lors des flambées de rougeole, dans le cadre de la délivrance intensifiée des services de vaccination: 2) pendant les AVS, dans les contextes ou le risque de rougeole chez les nourrissons reste important (pays d'endémie subissant régulièrement des flambées, par exemple): 3) dans le cas des populations déplacées à l'intérieur d'un même pays et des réfugiés ainsi que dans celui des populations vivant dans des zones de conflit: 4) dans la situation où des enfants sont exposés individuellement à un risque important de contracter la rougeole (contacts de cas connus de rougeole ou contextes comportant un risque accru d'exposition pendant les flambées comme les garderies pour enfants, par exemple): 5) dans le cas des nourrissons emmenés dans des pays où sévissent des flambées de rougeole: et 6) dans celui des nourrissons dont la positivité pour le VIH est connue (voir la note de synthèse sur le vaccin contre la rougeole de 2009).[11]

Comme, à cet âge, l'immunogénicité et l'efficacité de la vaccination sont plus faibles que pour les doses administrées à un stade ultérieur et compte tenu des préoccupations concernant l'efficacité à long terme d'un calendrier précoce en 2 doses, le vaccin MCV administré avant l'âge de 9 mois devra être considéré comme une dose supplémentaire et enregistré dans le dossier de vaccination de l'enfant comme une dose «MCV0». Les enfants recevant une dose MCV0 devront par la suite recevoir des vaccins à valence rougeole aux âges recommandés par le calendrier de vaccination national.

Les éléments disponibles sur l'innocuité et l'immunogénicité des vaccins contenant des valences rubéole et oreillons sont en faveur de leur utilisation à partir de 6 mois. Les pays utilisant le vaccin antirougeoleux-antirubéoleux (RR) ou le vaccin antirougeoleux antiourlien-antirubéoleux (ROR) dans leur calendrier national de vaccination devront faire appel au vaccin combiné plutôt qu'à des formulations ne contenant que la valence rougeole chez les enfants de <1 an. Le SAGE reconnaît qu'il s'agit d'un usage hors indication et recommande aux programmes nationaux de ne pas restreindre l'utilisation du vaccin à cette tranche d'âge. Il préconise d'autres études cliniques, immunologiques, épidémiologiques et de modélisation concernant l'impact des différents calendriers de vaccination antirougeoleuse.

L'analyse pour plusieurs pays de l'incidence des stratégies en matière d'AVS et la comparaison des données de surveillance et de susceptibilité en sont encore à leurs débuts. La modélisation mathématique laisse à penser que des AVS contre la rougeole de grande qualité (atteignant >90% des enfants susceptibles) à l'intention des enfants de <5 ans constituent une intervention d'une efficacité équivalente et d'un rapport coût/efficacité supérieur, par rapport à des AVS de moindre qualité, visant une gamme d'âge plus étendue (à l'intention des enfants de <10 ans et atteignant >70% des enfants susceptibles, par exemple). Un algorithme d'introduction des AVS utilisant le vaccin RR, destiné à guider les pays à propos des tranches d'âge à viser, semble prometteur. Des travaux supplémentaires sont nécessaires pour confirmer ses possibilités d'application et permettre une démarche intégrée antirougeoleuse-antirubéoleuse.

[11] Voir N° 35, 2009, pp. 349-360.

SAGE reviewed evidence indicating that an increasingly large number of HIV-infected children will receive antiretroviral therapy and that these children are at increased risk of measles because of poor antibody responses following vaccination prior to initiation of highly active antiretroviral therapy (HAART). While HAART does not restore measles immunity from previously received vaccine doses, it enables higher and more prolonged antibody responses following revaccination.

SAGE recommended that an additional dose of MCV be administered to HIV-infected children receiving HAART following immune reconstitution. If CD4+ T lymphocyte counts are being monitored, an additional dose of MCV should be administered when immune reconstitution has been achieved, e.g. when the CD4+ T lymphocyte count reaches 20%–25%. Where CD4+ T lymphocyte monitoring is not available, children should receive an additional dose of MCV 6–12 months after initiation of HAART. Current evidence is insufficient to recommend an additional dose for children who start HAART prior to the first dose of MCV.

A supplementary dose of MCV should be considered soon after diagnosis of HIV infection in children older than 6 months who are not receiving HAART, and for whom the risk of measles is high, with the aim of providing partial protection until they are revaccinated after immune reconstitution with HAART.

SAGE requested evidence on the need for measles revaccination of HIV-infected adolescents and adults. Further research is needed to monitor the long-term immune responses to measles vaccine in HIV-infected children revaccinated after starting HAART and in HIV-infected children starting HAART prior to receiving their first dose of MCV.

RTS,S/AS01 malaria vaccine

WHO recently estimated that 214 million new episodes of clinical malaria will have occurred during 2015 including 438 000 deaths, with most cases and deaths occurring in sub-Saharan Africa. Although this represents a tremendous burden of disease, there has been a substantial reduction in the last 15 years (over 50% for global malaria mortality in children aged <5 years) mainly due to greater investments in malaria control that have facilitated access to insecticide-treated nets, effective anti-malaria medicines and other tools. However, given the increasing problem of multi-drug resistance and insecticide resistance, there is still a need for new tools to combat malaria.

A large Phase 3 clinical trial of the RTS,S/AS01 vaccine has been completed involving approximately 15 000 infants and young children in 7 sub-Saharan African countries with a range of low to high malaria transmission settings. In the trial the vaccine was evaluated in 2 age categories – infants aged 6–12 weeks and infants aged 5–17 months at the start of the trial. In

Le SAGE a examiné des éléments indiquant qu'un nombre croissant d'enfants infectés par le VIH allaient recevoir un traitement antirétroviral et que ces enfants étaient exposés à un risque accru de rougeole du fait de leurs réponses en anticorps médiocres à la vaccination avant la mise en route du traitement antirétroviral hautement actif (HAART). Si le HAART ne rétablit pas ce que devrait être l'immunité contre la rougeole compte tenu des doses vaccinales précédemment reçues, il permet des réponses en anticorps plus fortes et plus prolongées après une revaccination.

Le SAGE a préconisé l'administration d'une dose supplémentaire de MCV aux enfants infectés par le VIH recevant le HAART une fois achevée la reconstitution immunitaire. Dans les cas où la numération des lymphocytes T CD4+ fait l'objet d'un suivi, on administrera une dose supplémentaire de MCV une fois la reconstitution immunitaire réalisée, par exemple lorsque le taux des lymphocytes T CD4+ atteint 20%-25%. Lorsqu'on ne dispose pas d'un tel suivi, les enfants devront recevoir une dose supplémentaire de MCV 6 à 12 mois après la mise en route du HAART. Les éléments actuellement disponibles sont insuffisants pour recommander une dose supplémentaire chez les enfants qui débutent le HAART avant la première dose de MCV.

Une dose additionnelle de MCV devra être envisagée peu de temps après le diagnostic d'une infection à VIH chez les enfants de >6 mois qui ne bénéficient pas du HAART et sont exposés à un risque important de rougeole, le but étant de leur procurer une protection partielle jusqu'à leur revaccination après reconstitution immunitaire avec le HAART.

Le SAGE a réclamé des données sur la nécessité de revacciner contre la rougeole les adolescents et les adultes infectés par le VIH. D'autres travaux de recherche sont nécessaires pour suivre les réponses immunitaires à long terme au vaccin antirougeoleux chez les enfants infectés par le VIH revaccinés après la mise en route du HAART et chez les enfants infectés par le VIH débutant ce traitement avant d'avoir reçu une première dose de MCV.

Vaccin antipaludique RTS,S/AS01

Selon une estimation récente de l'OMS, 214 millions de nouveaux épisodes de paludisme clinique seront intervenus pendant l'année 2015, s'accompagnant de 438 000 décès et d'une concentration des cas et des décès en Afrique subsaharienne. Si cela correspond à une charge de morbidité énorme, on a relevé un régression substantielle de cette charge au cours des 15 dernières années (>50% pour la mortalité mondiale due au paludisme chez les enfants de <5 ans), grâce, principalement, au renforcement des investissements dans la lutte contre le paludisme, qui ont facilité l'accès à des moustiquaires imprégnées d'insecticide, à des médicaments antipaludiques efficaces et à d'autres outils. Cependant, compte tenu de la problématique grandissante de la pharmacorésistance et de la résistance aux insecticides, il reste nécessaire de disposer de nouveaux outils pour combattre le paludisme.

Un large essai clinique de phase 3 du vaccin RTS,S/AS01 a été réalisé sur environ 15 000 nourrissons et jeunes enfants dans 7 pays d'Afrique subsaharienne offrant divers contextes de faible et forte transmission du paludisme. Dans le cadre de cet essai, le vaccin a été évalué dans 2 tranches d'âge: les nourrissons vaccinés à 6-12 semaines et les enfants âgés de 5-17 mois au début de l'essai. On comptait 3 groupes dans chaque tranche

each age category there were 3 groups: one group which received 3 doses of RTS,S vaccine at monthly intervals; a second group which received 3 doses of RTS,S vaccine followed by a 4th dose 18 months later; and a third control group which received 4 doses of a comparator vaccine. Control vaccines were the cell culture rabies vaccine (given to the infants in the 5–17 month category for the first 3 doses) or meningococcal serogroup C conjugate vaccine (given to the infants in the 6–12 week category for the first 3 doses, and to infants in both age categories for the 4th dose).

In both evaluated age categories, the trial showed moderate but significant protection against clinical malaria after 3 doses, waning substantially by 18 months. Protection was partially restored by a 4th RTS,S dose, given 18 months after the 3rd dose. During the full study period, in the 5–17 months age group that received the 4-dose schedule, vaccine efficacy against clinical malaria was 39.0% (95% CI: 34.3–43.3) and against severe malaria, 31.5% (95% CI: 9.3–48.3). Point estimates of vaccine efficacy in the older age category were lower in girls and in the younger age category they were lower in boys. Vaccine efficacy against all-cause hospitalization was 14.9% (95% CI: 3.6–24.8). The groups that received 4 doses of malaria vaccine experienced less clinical and severe malaria than those that received only 3 doses.

Based on the efficacy data from the Phase 3 trial, SAGE/MPAC does not recommend the use of the malaria vaccine in infants aged 6–12 weeks, as the vaccine efficacy was lower than in the infants aged 5–17 months.

In the 5–17 month age category, febrile seizures were identified as a vaccine adverse event (an additional 0.5 febrile convulsions per 1000 doses after the 3rd dose, and an additional 2 convulsions per 1000 doses after the 4th dose). Two potential safety signals were identified: a statistically significant increase in the number of meningitis and cerebral malaria cases in RTS,S vaccine groups compared to the control group (there was no sex difference in these adverse events). The presentation of all-cause mortality data by sex suggested a potential difference between female and male vaccine recipients.

RTS,S/AS01 received a positive regulatory assessment by the European Medicines Agency under Article 58,[12] indicating that the quality of the vaccine and the risk/benefit ratio are considered favourable from a regulatory perspective.

In settings of moderate to high transmission intensity and assuming a price of US$ 5 per dose, mathematical models predict the cost per DALY[13] averted to be less

d'âge: un groupe ayant reçu 3 doses du vaccin RTS,S à un mois d'intervalle; un second ayant reçu les 3 doses du vaccin RTS,S, suivies d'une 4e dose 18 mois plus tard; et un 3e groupe ayant reçu 4 doses d'un vaccin de comparaison. Les vaccins servant à la comparaison étaient le vaccin antirabique préparé sur culture cellulaire (administré aux enfants appartenant à la catégorie des 5-17 mois pour les 3 premières doses) et le vaccin antiméningococcique conjugué C (administré aux nourrissons vaccinés à partir de 6-12 semaines pour les 3 premières doses et aux 2 groupes pour la 4e dose).

Dans les 2 tranches d'âge évaluées, l'essai a mis en évidence une protection modérée, mais significative, contre le paludisme clinique après 3 doses, qui disparaissait substantiellement au bout de 18 mois. Cette protection était partiellement restaurée par une 4e dose de RTS,S, administrée 18 mois après la 3e dose. Sur l'ensemble de la période étudiée, dans la tranche d'âge ayant débuté la vaccination à 5-17 mois et ayant reçu le calendrier en 4 doses, l'efficacité vaccinale contre le paludisme clinique a été de 39,0% (IC à 95%: 34,3-43,3) et contre le paludisme sévère de 31,5% (IC à 95%: 9,3-48,3). Les estimations ponctuelles de l'efficacité vaccinale se sont révélées plus faibles chez les filles que chez les garçons parmi la catégorie plus âgée et inversement dans le groupe plus jeune. L'efficacité de la vaccination contre l'hospitalisation toutes causes confondues a été de 14,9% (IC à 95%: 3,6-24,8). Le groupe ayant reçu 4 doses de vaccin antipaludique a moins subi un paludisme clinique ou sévère que celui n'ayant reçu que 3 doses.

Au vu des données d'efficacité tirées de l'essai de phase 3, le SAGE et le MPAC ne recommandent pas l'emploi du vaccin antipaludique chez les nourrissons (vaccination à 6-12 semaines) car l'efficacité vaccinale s'est révélée plus faible dans cette catégorie que dans celle des 15-17 mois.

Dans la catégorie de nourrissons vaccinés à partir de 5-17 mois, on a identifié des convulsions fébriles en tant que manifestation vaccinale indésirable (0,5 cas supplémentaire de convulsions fébriles pour 1000 doses après la 3e dose et 2 cas de convulsions fébriles supplémentaires pour 1000 doses après la 4e dose). Deux signaux liés à la sécurité du vaccin ont été identifié: une augmentation statistiquement significative du nombre de cas de méningite et de paludisme cérébral dans les groupes ayant reçu le vaccin RTS,S par rapport au groupe témoin (on n'a relevé aucune différence en fonction du sexe pour ces événements indésirables). La présentation des données de mortalité toutes causes confondues par sexe a laissé entrevoir une différence potentielle entre les bénéficiaires féminins et masculins de la vaccination.

Le RTS,S/AS01 a bénéficié d'une évaluation réglementaire positive de la part de l'Agence européenne du médicament au terme de l'article 58,[12] qui indique que, dans le cadre de l'évaluation de ce vaccin par l'Agence, sa qualité et son rapport risque/bénéfice étaient apparus favorables d'un point de vue réglementaire.

Dans les contextes où la transmission est modérée à forte et en supposant un prix par dose de US$ 5, les modèles mathématiques prédisent un coût par DALY[13] évitée inférieur à

[12] Article 58 application: regulatory and procedural guidance. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000157.jsp; accessed November 2015.

[13] Disability adjusted life years.

[12] Article 58 application: regulatory and procedural guidance. Disponible à l'adresse: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000157.jsp; consulté en novembre 2015.

[13] Espérance de vie corrigée de l'incapacité.

than US$ 100, consistent with a highly cost-effective intervention and in a favourable range compared to other high impact vaccines. However, the models are based on cases prevented and do not incorporate the potential safety signals that emerged in the Phase 3 trial.

The primary outstanding question with regard to RTS,S/AS01 use in 5–17 month old infants is the extent to which the protection demonstrated in the Phase 3 trial can be replicated in the context of the routine health system, in view of the challenges involved in implementing a 4-dose schedule that requires new immunization contacts.

To address how best to ensure that 4 doses of malaria vaccine can be given between 5 and 27 months of age, SAGE/MPAC recommend evaluation of RTS,S in staged pilot implementations, addressing various knowledge gaps, before wider country level introduction can be considered.

Other questions that should be addressed as part of the pilot implementation include:

1. The extent to which RTS,S vaccination impacts mortality, which could not be adequately assessed in the Phase 3 trial due to the very low overall mortality in the trial setting.
2. Whether the excess cases of meningitis and cerebral malaria identified during the Phase 3 trial are causally related to RTS,S vaccination.

SAGE/MPAC recommend that the staged pilot implementations use the 4-dose schedule of the malaria vaccine in 3–5 distinct epidemiological settings in sub-Saharan Africa, at subnational level, covering moderate-to-high transmission settings, if possible including one with highly seasonal malaria. These pilot implementations should be done in phased designs and in the context of ongoing high coverage of other proven malaria control measures, particularly long-lasting insecticidal nets, access to rapid diagnostic tests and artemisinin-based combination therapy, and, where appropriate, seasonal malaria chemoprevention. Furthermore, alongside malaria vaccine delivery, the opportunity should be taken to include assessment of ways to strengthen the systems for delivery of effective child health services and immunization service delivery (including, where appropriate, new vaccine delivery such as PCV). These settings should involve sufficiently large populations followed for an adequate duration, with rigorous evaluation to allow:

- Assessment of operational feasibility of providing the malaria vaccine in the target age-group at the recommended schedule in the context of health service delivery in various countries;
- Evaluation of the impact of the vaccine on infant and child mortality, including measures to determine the impact of the vaccine when added to concomitant malaria interventions, by sex;

US$ 100, compatible avec un rapport coût/efficacité élevé de l'intervention et avec une plage de variation favorable, par rapport à d'autres vaccins ayant aussi un fort impact. Néanmoins, ces modèles se fondent sur les nombres de cas évités et ne prennent pas en compte les signaux liés à la sécurité potentiels qui mis en évidence au cours de l'essai de phase 3.

La principale question qui demeure non résolue à l'égard du to RTS,S/AS01 employé chez des jeunes enfants vaccinés à partir de 5-17 mois est la suivante: dans quelle mesure la protection mise en évidence dans l'essai de phase 3 peut être reproduite dans le cadre d'un système de santé ordinaire en raison des difficultés pour mettre en œuvre un calendrier en 4 doses nécessitant de nouveaux contacts vaccinaux.

Pour s'assurer au mieux de la possibilité d'administrer 4 doses de vaccin antipaludique entre 5 et 27 mois, le SAGE et le comité MPAC recommandent l'évaluation du RTS,S dans le cadre de mises en œuvre pilotes par étapes, en comblant les diverses lacunes en matière de connaissances avant d'envisager une introduction plus large à l'échelle nationale.

Parmi les autres questions auxquelles il convient de répondre par ces mises en œuvre pilotes, on peut notamment mentionner les points suivants.

1. L'ampleur de l'impact de la vaccination par le RTS,S sur la mortalité, qui n'avait pu être évalué correctement dans l'essai de phase 3 en raison de la très faible mortalité globale dans le cadre de cet essai.
2. L'existence d'une relation de causalité entre l'excès de cas de méningite et de paludisme cérébral repéré pendant l'essai de phase 3 et la vaccination par le RTS,S.

Le SAGE et le MPAC préconisent que les mises en œuvre pilotes par étapes appliquent le calendrier en 4 doses pour le vaccin antipaludique dans 3-5 contextes épidémiologiques distincts en Afrique subsaharienne, à un niveau infranational, en couvrant des zones de transmission modérée à forte, et si possible en incluant une zone où le paludisme sa manifeste de manière fortement saisonnière. Ces mises en œuvre pilotes devront s'effectuer par étapes et dans le contexte d'une forte couverture par d'autres mesures de lutte antipaludique ayant fait leurs preuves, notamment l'utilisation de moustiquaires imprégnées d'insecticide à effet rémanent, l'accès à des tests diagnostiques rapides et à un traitement combiné à base d'artémisinine, et, le cas échéant, à une chimioprévention saisonnière du paludisme. En outre, ces applications pilotes devront tirer parti de la possibilité, en parallèle avec la délivrance du vaccin antipaludique, d'inclure dans l'intervention des moyens d'accès pour renforcer les systèmes dispensant des soins de santé à l'intention des enfants et des services de vaccination efficaces (y compris, si nécessaire, la délivrance de nouveaux vaccins comme le PCV). Les contextes dans lesquels sera opérée la mise en œuvre devront abriter des populations suffisamment importantes et faisant l'objet d'un suivi suffisamment long et d'une évaluation rigoureuse pour permettre:

- l'évaluation de la faisabilité opérationnelle de la fourniture du vaccin antipaludique à la tranche d'âge cible selon le calendrier recommandé dans le cadre de la prestation des services de santé dans divers pays;
- l'évaluation de l'impact du vaccin sur la mortalité infanto-juvénile, y compris des mesures de cet impact lors de l'association du vaccin à d'autres interventions antipaludiques concomitantes, en fonction du sexe;

- Real-time monitoring of adverse events following immunization, with causality assessment of meningitis and cerebral malaria, using pre-specified case definitions, by sex;
- The systematic compilation of evidence on the functioning of the immunization programme, broader health system functioning and community engagement.

SAGE/MPAC strongly recommends that WHO oversees the design and evaluation of these pilot implementations and monitors the emerging findings. SAGE/MPAC request continued review of the planning of the pilot implementations and to receive regular updates on the results. SAGE/MPAC emphasized the importance of maximizing the rigour of the pilot implementations to address the above issues, so that information on which to make decisions about expanded use of the vaccine can be generated as early as possible.

Prior to any pilot implementation appropriate communication materials should be developed and disseminated with particular emphasis on the partial efficacy of the vaccine, the importance of the 4th dose, the need for the continued/increased application of existing malaria control measures, as well as the importance of evaluating safety signals.

SAGE/MPAC also identified the following additional research needs:

- Evaluation of whether a 5th dose of RTS,S/AS01 is needed to protect against a potential rebound after the 4th dose;
- Monitoring possible emergence of vaccine-resistant strains following large-scale use of the vaccine;
- Exploration of alternative schedules and other strategies to improve the efficacy and safety of the RTS,S vaccine;
- Clinical trial evaluation of the RTS,S vaccine in the context of elimination, including studies evaluating safety and efficacy against infection over a wide age range; a high priority area for such an evaluation is South-East Asia in areas of artemisinin resistance;
- Impact of HIV infection on vaccine efficacy and duration of protection;
- Impact of RTS,S vaccine deployment on the utilization of other malaria control interventions;
- Impact of RTS,S vaccine deployment on EPI coverage;
- Evaluation of the efficiency of different communication strategies in terms of improving vaccine coverage and effectiveness.

Global Vaccine Action Plan (GVAP) 2015: assessment of progress and recommendations

The independent assessment of progress towards the GVAP goals[14] and strategic objectives followed the process laid out in the Monitoring, Evaluation and

- le suivi en temps réel des manifestations postvaccinales indésirables, avec une évaluation du lien de causalité pour les cas de méningite et de paludisme cérébral, en utilisant des définitions de cas préspécifiées, en fonction du sexe;
- la compilation systématique des données sur le fonctionnement du programme de vaccination et du système de santé plus largement et sur l'engagement des communautés.

Le SAGE et le MPAC recommandent fortement que l'OMS supervise ces mises en œuvre pilotes et suive les résultats qui en ressortent. Il réclame un suivi continu de la planification de ces mises en œuvre et à recevoir des actualisations régulières des résultats. Le SAGE et le MPAC soulignent l'importance de réaliser les mises en œuvre pilotes avec une rigueur maximale pour répondre aux questions précédemment énoncées, en vue d'être en mesure de générer, dès que possible, des informations sur l'usage étendu du vaccin qui permettent de prendre des décisions.

Avant toute mise en œuvre pilote, du matériel de communication approprié devra être mis au point et diffusé, en insistant tout particulièrement sur l'efficacité partielle du vaccin, l'importance de la 4e dose, la nécessité de poursuivre et d'étendre l'application des mesures existantes de lutte contre le paludisme et l'importance d'évaluer les signaux liés à la sécurité.

Le SAGE et le MPAC ont également identifié les besoins suivants en termes de recherches supplémentaires:

- évaluation de la nécessité d'une 5e dose de RTS,S/AS01 pour protéger contre un éventuel rebond de la sensibilité après la 4e dose;
- surveillance de l'émergence possible de souches résistantes au vaccin suite à un usage à grande échelle de celui-ci;
- étude d'autres options en matière de calendrier et d'autres stratégies pour améliorer l'efficacité et l'innocuité du vaccin RTS,S;
- évaluation par des essais cliniques du vaccin RTS,S dans un contexte où l'on vise l'élimination, avec notamment des études pour apprécier son innocuité et son efficacité contre l'infection dans une gamme d'âge étendue; les zones d'Asie du Sud-Est où se manifeste une résistance à l'artémisinine devraient être fortement prioritaires pour cette évaluation;
- impact de l'infection à VIH sur l'efficacité vaccinale et la durée de la protection apportée;
- impact du déploiement du vaccin RTS, sur la mise en œuvre d'autres interventions de lutte contre le paludisme;
- impact du déploiement du vaccin RTS,S sur la couverture par le Programme élargi de vaccination;
- évaluation de l'efficacité de différentes stratégies de communication en termes d'amélioration de la couverture et de l'efficacité vaccinales.

Plan d'action mondial pour les vaccins (GVAP) 2015: évaluation des progrès et recommandations

L'évaluation indépendante des progrès vers les buts[14] et les objectifs stratégiques du GVAP a fait suite au processus défini dans le cadre de suivi, d'évaluation et de responsabilisation et

[14] See http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/; accessed October 2015.

[14] Voir http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/; consulté en octobre 2015.

Accountability Framework and builds on the GVAP secretariat report[15] on progress towards each of the GVAP indicators. The salient findings of this year SAGE GVAP assessment report[16] and the main recommendations made by SAGE are briefly summarized below.

A year ago, SAGE published a report critical of the progress being made towards the GVAP goals, and it cannot be expected that the major indicators will have changed substantially since then as the data collection process and outcome changes take time to become evident.

Performance against key immunization targets remains off-track, although there have been some successes. These isolated improvements in countries and at the global level as highlighted below will have to become the norm if the plan is to get back on track.

- The GVAP target for introduction of new or underutilized vaccines is on track worldwide, with 86 low- and middle-income countries introducing 128 vaccines since 2010.
- The Ebola candidate vaccines were developed and tested within a short time frame and showed potential to protect against a high mortality disease.
- To date, 40 countries have shared information on vaccine pricing with WHO compared with only 1 last year.[17]
- India has been declared as having eliminated of maternal and neonatal tetanus, demonstrating that disease elimination is possible even in challenging circumstances.
- Africa has not had a case of poliomyelitis due to wild poliovirus since August 2014 – an enormous achievement.
- The Americas became the first region to eliminate rubella and congenital rubella syndrome, a major achievement.

In its third report,[16] SAGE focused on the need for leadership and accountability systems at all levels, particularly within countries, to put implementation of the GVAP back on track. Based on countries' achievements, SAGE identified the following common factors that would lead to success: improving quality and use of data; community involvement; improved access to immunization services for marginalized and displaced populations; strengthening health systems; securing and sustaining supply of vaccines at all levels; and leadership and accountability.

SAGE concurred with the main conclusions from the working group and made the recommendations listed below.

s'est appuyée sur le rapport du secrétariat du GVAP[15] concernant la progression de chacun des indicateurs du Plan d'action. Les résultats saillants du rapport d'évaluation SAGE GVAP de cette année[16] et les principales recommandations émises par le SAGE sont brièvement résumées ci-après.

Un an auparavant, le SAGE avait publié un rapport critique des progrès faits en direction des buts du GVAP, on ne devrait pas s'attendre à ce que les indicateurs principaux aient subi des changements substantiels entre temps, car le processus de recueil des données et l'évolution des résultats prennent du temps avant de révéler une tendance.

Par rapport aux principales cibles en termes de vaccination, les performances restent largement en deçà des attentes, malgré quelques succès. Ces améliorations isolées dans certains pays et à l'échelle mondiale, comme souligné ci-après, devront devenir la norme si l'on veut que le Plan d'action reprenne la voie de la réalisation.

- La cible du GVAP relative à l'introduction de vaccins nouveaux ou sous-utilisés est en bonne voie de réalisation au niveau mondial, avec 86 pays à revenu faible ou intermédiaire ayant introduit 128 vaccins depuis 2010.
- Des vaccins candidats contre la maladie à virus Ebola ont été mis au point et testés dans un court laps de temps et ont fait la preuve d'un potentiel de protection contre cette maladie responsable d'une forte mortalité.
- À ce jour, 40 pays ont communiqué à l'OMS des informations sur la fixation des prix des vaccins, contre seulement un l'année précédente.[17]
- L'Inde a été déclarée comme ayant éliminé le tétanos maternel et néonatal, ce qui démontre que l'élimination de cette maladie est possible même dans des circonstances difficiles.
- L'Afrique n'a enregistré aucun cas de poliomyélite dû de poliovirus sauvage depuis août 2014 – un succès énorme.
- Les Amériques représentent maintenant la première région à avoir éliminé la rubéole et le syndrome rubéoleux congénital, une réalisation de premier plan.

Dans ce 3e rapport,[16] le SAGE s'est concentré sur la nécessité d'un encadrement et de dispositifs de responsabilisation à tous les niveaux, en particulier au sein des pays, pour remettre le plan d'action GVAP sur la voie de ses objectifs. Sur la base des résultats des pays, le SAGE a identifié les facteurs communs suivants, qui devraient conduire au succès: amélioration de la qualité et de l'exploitation des données; implication des communautés; amélioration de l'accès aux services de vaccination pour les populations marginalisées ou déplacées; renforcement des systèmes de santé; constitution et maintien d'approvisionnements en vaccins à tous les niveaux: et encadrement et responsabilisation.

Le SAGE a exprimé son accord avec les principales conclusions du groupe de travail et a recommandé les points suivants.

[15] See http://www.who.int/entity/immunization/global_vaccine_action_plan/gvap_secretariat_report_2015.pdf?ua=1; accessed 2015

[16] See http://www.who.int/immunization/global_vaccine_action_plan/en/; accessed October 2015.

[17] See http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R6-en.pdf; accessed October 2015.

[15] Voir http://www.who.int/entity/immunization/global_vaccine_action_plan/gvap_secretariat_report_2015.pdf?ua=1; consulté en 2015.

[16] Voir http://www.who.int/immunization/global_vaccine_action_plan/en/; consulté en octobre 2015.

[17] Voir http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R6-en.pdf; consulté en octobre 2015.

To improve accountability to achieve the GVAP goals:

1. Countries have annual plans for immunization consistent with the GVAP and relevant regional vaccine action plans. The Ministries of Health, Finance and other pertinent ministries demonstrate leadership by establishing an annual process for monitoring and accountability at national and subnational levels. Monitoring should be through an independent body, e.g. the NITAG. Each country should share, every year, with WHO regional offices, its monitoring report which should include monitoring progress towards achievement of outcomes and sharing of best practices.

2. Once regional vaccine action plans are finalised (by December 2015), WHO regional offices should establish a process of annual progress review through their regional technical advisory groups and report to the respective Regional Committees. The first annual review should take place in the first half of 2016 for countries which already have annual plans consistent with the GVAP. WHO Regional Committees' reports should be made available annually to SAGE as part of the global review process.

3. Global, regional and national development partners should align their efforts to support countries in strengthening their leadership and accountability frameworks and in implementing their national plans. This should include establishing and/or strengthening partner coordination mechanisms at each level.

4. Decade of Vaccines secretariat agencies should report to SAGE in 2016 on their supporting activities conducted in the 10 countries where most of the unvaccinated and under-vaccinated children live. This annual reporting mechanism should include discussion of those reports in regional technical advisory groups.

To address the shortfalls in disease-specific areas of the GVAP's implementation:

5. Given poor progress with elimination of maternal and neonatal tetanus and the relatively small funding gap to achieve this goal, WHO and UNICEF should convene a meeting of global partners and the remaining 21 countries to agree on an action plan, resources and respective responsibilities so that the goal is achieved no later than 2017, and that thereafter strategies are in place to sustain elimination in all countries.

6. Global, regional and national development partners should support countries in securing the required resources and in implementing their measles and rubella elimination or control strategies and plans. The recommendations of the mid-term review of the global measles and rubella strategic plan to be conducted in 2016, once endorsed by SAGE, should be taken into account in refining plans and for monitoring and enhancing quality of implementation.

Une plus grande responsabilisation des acteurs pour atteindre les buts du GVAP.

1. Les pays disposent de plans annuels pour la vaccination compatibles avec le GVAP et de plans d'action régionaux pour les vaccins pertinents. Les ministères de la santé et des finances et d'autres ministères concernés exercent leur rôle directeur en mettant en place un processus annuel de suivi et de responsabilisation aux niveaux national et infranational. Ce suivi devra s'effectuer par l'intermédiaire d'un organisme indépendant, par exemple les groupes consultatifs techniques nationaux sur la vaccination. Chaque pays devra communiquer, chaque année, aux bureaux régionaux de l'OMS son rapport de suivi, mentionnant les progrès enregistrés vers la réalisation des résultats et également en faire part des meilleures pratiques.

2. Une fois les plans d'action régionaux finalisés (d'ici décembre 2015), les bureaux régionaux de l'OMS mettront en place un processus d'examen des progrès annuels par le biais de groupes consultatifs techniques régionaux et feront rapport aux comités régionaux respectifs. Le premier examen annuel devrait avoir lieu au cours de la première moitié de l'année 2016 pour les pays disposant déjà de plans annuels compatibles avec le GVAP. Les rapports des comités régionaux de l'OMS devront être mis chaque année à la disposition du SAGE dans le cadre du processus d'examen mondial.

3. Les partenaires mondiaux, régionaux et nationaux du développement devront aligner leurs efforts pour appuyer les pays dans le renforcement de leurs cadres de direction et de responsabilisation et dans la mise en œuvre de leurs plans nationaux. Ces efforts devraient inclure l'instauration et/ou le renforcement de mécanismes de coordination entre les partenaires à chaque niveau.

4. Les agences du secrétariat de la Décennie des vaccins devront rendre compte au SAGE en 2016 de leurs activités de soutien menées dans 10 pays où vivent la plupart des enfants non vaccinés ou sous-vaccinés. Ce mécanisme annuel de compte rendu devrait inclure la discussion des rapports au sein des groupes consultatifs techniques régionaux.

Pour faire face aux insuffisances dans des domaines spécifiques à des maladies de la mise en œuvre du GVAP:

5. Compte tenu des progrès médiocres dans l'élimination du tétanos maternel et néonatal et des lacunes relativement limitées du financement à cette fin, l'OMS et l'UNICEF devront réunir les partenaires mondiaux et les 21 pays restants pour convenir d'un plan d'action, des ressources nécessaires et des responsabilités respectives afin que les objectifs soient réalisés d'ici 2017 au plus tard et qu'ensuite des stratégies soient en place pour maintenir l'élimination dans l'ensemble des pays.

6. Des partenaires mondiaux, régionaux et nationaux au développement devront aider les pays à se procurer les ressources nécessaires et à mettre en œuvre leurs stratégies et leurs plans pour éliminer ou combattre la rougeole et la rubéole. Les recommandations formulées à l'issue de l'examen à mi-parcours du plan stratégique mondial contre la rougeole et la rubéole, prévu en 2016, une fois approuvées par le SAGE, devront être prises en compte pour affiner les plans et pour suivre et améliorer la qualité de l'application de ces plans.

To improve immunization coverage especially where many unvaccinated and under-vaccinated children live, including those affected by conflict and crisis:

7. Global, regional and country development partners should coordinate and align their efforts to support countries to immunize more children by strengthening their health-care delivery systems, combined with targeted approaches to reach children consistently missed by the routine delivery system, particularly in the countries where vaccination rates, or subnational rates in larger countries, are <80% and to provide services to populations displaced due to conflict (both internally displaced persons and refugees).

8. WHO should provide guidance for countries and partners on implementation of immunization programmes and immunization strategies during situations of conflict and chronic social disruption.

The 2016 GVAP assessment report will serve as a mid-term review of progress in the Decade of Vaccines and SAGE recommends that this report be presented at the World Economic Forum in Davos, where the Decade of Vaccines was launched. The 2016 report should aim to highlight the game-changers at global, regional, and country levels.

Report on activities from international immunization partners

During this meeting, a series of presentations on immunization-related activities of partners working and contributing to the GVAP implementation was initiated.

UNICEF presented its work on data acquisition and analysis, humanitarian emergencies, sustainable financing for vaccines and other products, supply chains, procurement, and vaccine and other health-related communications.

Médecins Sans Frontières (MSF) outlined their work on vaccination activities within routine immunization programmes and in humanitarian emergencies, their outbreak response work, and research and advocacy activities.

SAGE was appreciative of the start of this series of presentations, highlighting the importance of hearing from global stakeholders and partners in the field of immunization. SAGE applauded both organizations for their work and stressed continuous efforts to ensure collaboration between WHO and partner agencies including non-governmental organizations.

SAGE stressed the necessity to assess how immunization activities can be carried out in the context of response to humanitarian emergencies, and called for strengthened collaboration between the GAVI Alliance, UNICEF, MSF and other involved organizations to facilitate prompt provision of vaccines to the most vulnerable populations. ■

Pour renforcer la couverture vaccinale, en particulier dans les zones où vivent de nombreux enfants non vaccinés ou sous-vaccinés, y compris celles touchées par des conflits ou des crises:

7. Les partenaires mondiaux, régionaux et nationaux au développement devront coordonner et aligner leurs efforts pour aider les pays à vacciner davantage d'enfants en renforçant leurs systèmes de prestation des soins de santé, effort qu'il faudra combiner à des approches ciblées pour atteindre les enfants régulièrement laissés de côté par le système habituel de vaccination, notamment dans les pays où les taux nationaux de vaccination, ou encore les taux infranationaux dans des pays plus étendus, sont inférieurs à 80%, ainsi que pour apporter ces services aux populations déplacées en raison de conflits (à la fois aux personnes déplacées à l'intérieur du pays et aux réfugiés).

8. L'OMS devra fournir des orientations aux pays et aux partenaires concernant la mise en œuvre des programmes et des stratégies de vaccination dans les situations de conflits et de troubles sociaux chroniques.

Le rapport d'évaluation du GVAP pour l'année 2016 servira d'examen à mi-parcours des progrès dans la Décennie des vaccins et le SAGE préconise que ce rapport soit présenté au Forum économique mondial de Davos où la Décennie des vaccins a été initiée. Ce rapport 2016 devra s'efforcer de mettre en lumière les éléments susceptibles de changer la donne aux niveaux mondial, régional et national.

Rapport d'activités des partenaires internationaux dans les actions de vaccination

Pendant cette réunion, une série de présentations sur les activités liées à la vaccination des partenaires collaborant et contribuant à la mise en œuvre du GVAP a été lancée.

L'UNICEF a présenté son travail sur l'acquisition et l'analyse de données, les urgences humanitaires, le financement durable des vaccins et d'autres produits, les chaînes d'approvisionnements et les achats, ainsi que les communications relatives aux vaccins et à d'autres sujets sanitaires.

L'organisation Médecins sans frontières (MSF) a exposé dans leurs grandes lignes son travail sur les activités de vaccination dans le cadre des programmes de vaccination systématique et des urgences humanitaires, ses actions de réponses aux flambées épidémiques et ses activités de recherche et de plaidoyer.

Le SAGE a vivement apprécié le début de la série de présentations, mettant l'accent sur l'importance d'être à l'écoute des parties prenantes et des partenaires mondiaux dans le domaine de la vaccination. Il a félicité les 2 organisations pour leur travail et a souligné les efforts continus pour garantir la collaboration entre l'OMS et les organismes partenaires, y compris avec les organisations non gouvernementales.

Le SAGE a souligné la nécessité d'évaluer comment les activités de vaccination peuvent être menées dans le contexte de la réponse aux urgences humanitaires et a appelé à renforcer la collaboration entre l'Alliance GAVI, l'UNICEF, MSF et d'autres organisations partenaires pour faciliter un approvisionnement sans délai en vaccins des populations les plus vulnérables. ■

SAGE TRACKING RECORD OF RECOMMENDATIONS AND ACTION POINTS

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

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

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

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
General	SAGE 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 review paper on the Global Advisory Committe on Vaccine Safety (GACVS) future is currently under preparation and will address this issue in particular. The final paper has been submitted to a peer-reviewed journal end of 2015, though there has not been any reply so far.
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 EPI is working on. Subsequently, in early June a draft typology was produced and shared that summarizes this area of work. The topic was discussed at the April 2014 SAGE meeting. SAGE concluded that addressing integration, by its very nature, requires a broader discussion beyond SAGE. In this regard, it was proposed that the SAGE working group on the Decade of Vaccines (DoV) consider options for moving forward, as integration is reflected as both a guiding principle and a strategic objective of the Global Vaccine Action Plan (GVAP). The Department secured funding at the end of 2014 to establish a position dedicated to the issue of integration. Recruitment has been completed and the recruited staff started in October 2015. A session on implementation/integration will be held at the April 2016 SAGE meeting.
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 first country assessment planned in this project, Zambia, has been completed by the consultant, Rebecca Fields from JSI. It was incorporated into the existing country strategies to improve the routine immunization delivery in the second year of life, and will be used in the development of the WHO guidance on this matter. UNICEF is completed a landscape analysis of this area of work and presented their findings at the Global Vaccine and Implementation Research Forum (GVIRF) in March in Johannesburg, South Africa. A Second year of life platform session is on the agenda of the April 2016 SAGE meeting.
General	SAGE recommended that ways to improve curricula for medical personnel should be explored.	Nov 2008	Ongoing	This area of worked has been stalling as the main person steering this work, retired 2 years back. AFRO has not been able to find a replacement for capacity building work. Only limited work has been happening in other regions in this area.
General	SAGE stressed that additional disaggregation was needed in the analysis of the progress achieved on the ground, and in identifying bottlenecks for progress, and recommended that reports display disparities observed at sub-national levels.	Apr 2015	Ongoing	WHO HQ is working closely with regional offices to obtain subnational level data. Surveillance data for measles and rubella as well as for new vaccines is collected on district level on regular basic and there are efforts to collect sub-national level coverage data. Currently this is happening in AFR on monthly as well as annual basis and in SEAR and EUR on an annual basis.

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 would 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. Guidelines on procedures and data requirements for changes to approved vaccines were adopted by ECBS in October 2014 (TRS 993, annex 4). Preliminary consultations took place around the 2015 ECBS meeting for specific guidance on Labelling information of inactivated flu vaccines for use in pregnant women. This document is subject of public consultation until 19 February 2016 and it is hoped that the document will be finalized during the 2016 ECBS meeting. A paper clarifying the differences between regulatory decisions and public health recommendations has been commissioned. Unfortunately there have been sustained protracted delays in finalization of the publication. This submission process for this paper has been initiated at the beginning of March 2016.
Administrative matter	Members asked that a clarification of what members were asked to report (i.e. what directly concerns their department or the departments under their line of authority) be included in the web posting of the Declarations of Interests summary in the future.	Apr 2015	Completed	This was followed up with WHO Ethics and Compliance Department. It was specified that SAGE members would need to report only interests directly linked with their respective research unit as sub-unit of a department and not the entire department or institution. A brief on the process for declaring and assessing interests of SAGE members was posted on the WHO SAGE website.
Agenda item	SAGE requested a discussion on the global shortage of vaccines at the next meeting.	Apr 2015	Ongoing	After some delay, a session on preempting and responding to vaccine shortages is scheduled for the April 2016 SAGE meeting.
Decade of vaccines/GVAP	The SAGE working group should continuously review the need for reformulation of the indicators or mechanisms for collection and reporting of data.	Nov 2012	Ongoing	The SAGE report of progress with the Global Vaccine Action Plan (GVAP) for 2015 was published online and is available at:http://www.who.int/immunization/global_vaccine_action_plan/en/ This report was tabled at the Executive Board in January 2016 and will be tables with the comments received from the EB tabled at the WHA in May 2016. Preparations have begun for preparing the 2016 progress 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. In June 2015 IVIR-AC reviewed the DOVE project. More information can be found in the IVIR-AC recommendations 2015.
Decade of vaccines/GVAP	SAGE recommended that the 2016 GVAP assessment report be presented at the World Economic Forum in Davos where the Decade of Vaccines was launched.	Oct 2015	Ongoing	The recommendation made at the October 2015 SAGE meeting arrived too late to include to the Davos 2016 agenda. Therefore, it has been agreed with DoV partner agencies to include at World Economic Forum in Davos in January 2017. It will allow us to share the 2016 mid-term SAGE assessment report and also to be able to include some inputs from both SAGE recommendations on MNTE and Measles-Rubella Elimination revised strategies (to be presented to SAGE in October 2016).

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Dengue	A SAGE dengue working group should be convened to revise the data and prepare recommendations to SAGE as clinical trial data is expected to be submitted to the regulatory authorities in early 2015.	Oct 2014	Ongoing	The SAGE Working Group on Dengue Vaccines was constituted and held monthly teleconferences. Two face-to-face meetings of thewere held 23-25 September 2015 and 10-11 February 2016. The SAGE session for decision will take place on 14 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) has reviewed the company's risk management plan at its June 2015 meeting. This material will inform the SAGE WG in preparation for the April 2016 SAGE meeting.
Ebola vaccines	Noting WHO's unique position to coordinate the development of Ebola vaccines, SAGE stressed the importance of transparent and prompt sharing of information on the trial protocols and data from the phase 3 clinical trials, and the need for a greater role for WHO in facilitating the sharing of information so that results between studies will generate the greatest benefit for policy decision-making.	Apr 2015	Ongoing	The paper published in the Lancet " Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomized trial." was shared with SAGE members. The positive results of the trial prompted SAGE to schedule an extraordinary teleconference mid- August after the SAGE Ebola Working Group meeting to discuss the further steps and the possible need for a preliminary statement/recommendation from SAGE. The Working Group presented to SAGE in October 2015. Regulatory evaluation of the vaccine is currently ongoing. At this stage, there are no new peer-reviewed data and the trials are still ongoing.
Ebola vaccines	SAGE was asked to immediately establish a SAGE working group on Ebola vaccines and vaccination.	Oct 2014	Ongoing	The working group (WG) was established and has met regularly via teleconference. A face-to-face meeting of the WG took place on March 9 and 10, 2015. The WG reviewed the current 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 was presented to SAGE at the April 2015 meeting. The SAGE working group met again on August 19-20 in Geneva to review the available information and begin to start framing recommendations, based on the framework approved by SAGE in April 2015. The working group input was presented to SAGE at the October 2015 meeting. Currently the Working Group is awaiting new evidence from the clinical trials and regulatory approval of the vaccie before revising the topic and issuing draft recommendations.
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 February 2016. 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 compatible with very high vaccine effectiveness. The situation continues to be investigated. Hepatitis A cases have remained low in 2014 and 2015. Although a reduction in hepatitis A rates was experienced in all age groups, there is an increasing proportion of the remaining cases occurring in persons > 14 years of age in the post vaccination period. Most of these represent non-vaccinated adolescents or adults that escaped HAV-infection in previous outbreaks. Regarding children with a confirmed HAV-acute infection, many are unvaccinated children arriving from Bolivia where HAV vaccine is not included in the regular calendar. As exemplified by the outbreak in San Martin the risk persists in the population. 73% of of HAV acute infection cases reported occurred in individuals over >10 years. All cases reported occurred in unvaccinated individuals. Both Colombia and Paraguay also introduced a single dose national immunization schedule for 1 year old children. Yearly review of the Argentina surveillance data will continue as Argentina was the front runner country to introduce a 1 dose schedule with the inactivated vaccine. A third phase immunogenicity study is undergoing in Argentina, to assess long term protective antibodies in children more than 9 years following single dose vaccination. So far the results of the phase two study conducted in 2013 and with a median post-vaccination interval of 7.7 years have been quite reassuring with 97.4% (95% CI: 96.3-98.3).

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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	The Eastern Mediterranean Region (EMR) has a Regional Committee (RC) goal of reducing childhood hepatitis B prevalence to <1% among children <5 years by 2015. Its regional office, EMRO is working with Member States to ensure achievement of this goal. The Western Pacific Region (WPR) established a Regional Committee goal to reduce hepatitis B infection to <1% among children at least 5 years of age by 2017. The South East Asian Regional Office (SEARO) has a drafted regional strategy. An HQ mission to discuss HepB control targets took place in Aug 2015. The African Regional Office (AFRO) convened a regional hepatitis Technical Advisory Group (TAG) and presented 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 and adopted hep B activities as part of the RVAP that was also endorsed at the same RC meeting. The European Regional Office (EURO) will consider a regional hepatitis B control goal as proposed by ETAGE. The Pan American Health Organization (PAHO) has resolved to eliminate hepatitis B virus transmission and is formulating a regional strategy. Documenting the Impact of Hepatitis B Immunization: best practices for conducting a serosurvey (WHO/IVB/11.08) was published in 2011 by the department of Immunization, Vaccines and Biologicals. In 2012, WHO HQ has published a framework for global action to control viral hepatitis (http://www.who.int/csr/disease/hepatitis/Framework/en/index.html). The 2016 WHO Executive Board approved a global health sector strategy on viral hepatitis 2016-2021 that proposes an impact target of less than 1% HBsAg prevalence among children by 2020 and 0.1% by 2030.
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 countries to jointly propose actions towards improving birth dose uptake. In Jan 2015 the African Regional Office AFRO, and in March 2015 WPRO, held Hep B birth dose consultations to improve birth dose coverage. An assessment of BD implementation has taken place in Sao Tome Principe in July 2015 and Nigeria in September 2015 and in the Gambia in December 2015. Senegal held a Hep B birth dose training workshop in Dec and introduced birth dose in January 2016. Guidance for Hep B birth dose introduction have been cleared for publication and should be available in Q1 2016.

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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. We now understand that the South African trial will be a Phase 2b trial rather than a Phase 3 trial, and is scheduled to start in late 2016. 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.
Immunization schedules	SAGE requested that IVIR-ACassess optimal immunization schedules based on both direct and indirect effects and not only direct effects.	Oct 2015	Ongoing	As part of any vaccine impact evaluation IVIR-AC reviews and encourages studies of optimal schedules on both direct and indirect effects. Study projects and meetings have been held and are planned on HPV, Hep B vaccines, rotavirus vaccines among others.
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) was presented to SAGE in April 2015, with a focus on Pertussis leading to the update of the Pertussis Position Paper, published in August 2015. Evidence on Hep B vaccines will be presented at the October 2016 meeting - delays due to impact of Ebola outbreak. Further current ongoing work is a review of emerging evidence on HPV vaccination including the 9-valent vaccine and vaccination of boys as well as a review of the impact of vaccination schedules.
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 develop a revised version of the Effective Vaccine Management (EVM) assessment tool for it to become an assessment that covers broader immunization supply chain and logistics aspects beyond vaccine management policies and practise. Since this is a significant undertaking and a time consuming one, the approach in 2015 is to include additional data collection and/or assessment modules for Human Resources alongside the existing approach to EVM assessments. This Human Resource module is being developed by UNICEF Supply Division under the auspices of the People that Deliver (PtD) initiative 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.

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Immunization Supply Chains	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.
Implementation	SAGE recommended the formation of an implementation group that had a broad array of expertise in this area.	Apr 2015	Pending	A document on applying rigour and science in implementation programme design and evaluation of delivery of vaccines was drafted by SAGE members. This document was then discussed by WHO/IVB. It was agree that as a first step, instead of forming a SAGE working group, the Director of the Department of Immunization, Vaccines and Biologicals will work with the WHO health systems strengthening (HSS) group and have them come to the feedback presented at the April 2016 SAGE meeting in order to look at what is being done in the context of universal health care. Then, it will be decided if a SAGE or extended working group is needed. A session on implementation is scheduled for the April 2016 SAGE meeting and the main WHO focal point for the session is from HSS.
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. Since 2014 research topics on the non-specific effects of vaccines, missed opportunities and community vaccine acceptance have been been part of the agenda of IVIR-AC.
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 June 2015 meeting of the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) meeting agreed on the plan for phase 1 of the comparison of pertussis models from Australia, England & Wales and the United States of America, which is meant to be a rapid assessment on the relative contributions of vaccine formulations, waning immunity, vaccine coverage and schedule to observed pertussis resurgence in these countries. If successful, phase 2 offers further opportunities to test whether existing models are sufficiently robust to changes in factors such as demographics, spatial heterogeneity, immunity and contact matrices across multiple settings. In many countries using aP vaccine in the national immunization programme, aP vaccine is used in the private sector which represents a variable proportion of infant immunizations, so these complexities will need to be reflected when the models are extended to low and middle income settings. Phase 1 has been implemented and preparations are under development for Phase 2 and implementation will depend on funds being made available. Pertussis surveillance and laboratory capacity are still extremely poor in LIMCs particularly in Africa), and beyond the scope of the model comparison exercise to address. The committee noted that data are expected to be forthcoming through ongoing studies and follow-on analysis of maternal influenza trials, and strongly endorses the identification or further opportunities to add pertussis markers (primarily PCR on respiratory specimens) to studies such as GAVI– or the BMGF– supported vaccine impact studies. There were concerns that the opportunistic process by which the 3 models were identified may not have included all relevant parameters or modelling approaches. The feasibility of taking into account other models and parameters identified through a literature review and/or open call should be assessed, focusing on the main results of the different models for phase 1, and if they are interested to include them in phase 2.

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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) of June 2015 meetings, the need to develop standardized protocols for randomized controlled trials on non-specific effects of vaccines (NSE) was highlighted. Two IVIR-AC members volunteered to follow up this work. On 16–17 February 2016, IVR convened an ad-hoc expert consultation on NSE clinical trials. Eighteen experts (including 3 IVIR-AC members) contributed to this consultation, whose main objectives were to reach a consensus on priority trial questions and to propose trial designs for each of the priority questions. Protocol synopses for the six different trials that the experts proposed are being prepared for review and discussion at June 2016's IVIR-AC meeting.
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	A session to update SAGE on this area of work is planned for the April 2016 SAGE Meeting. Based on the two Missed Opportunity Assessments (MOV) conducted in Chad and Malawi in 2015 (draft manuscripts prepared for peer reviewed journal submission), the package of methodology materials will be finalized by June. These include: main assessment guide, health facility intervention guide, the MOV protocol, sample questionnaires and generic field guides. Having strengthened the capacity of AFRO to implement MOV assessments (discussions with Kenya are ongoing), collaboration is now beginning in 2016 with SEARO where MOV assessments are being planned and supported in Indonesia and Timor Leste. To establish a network of partners engaged in MOV, an informal coordination meeting is being planned for April 2016 to provide briefing on the process and outcomes of the recent country MOV assessments, share future plans and framework for implementation, and achieve consensus on a coordination mechanism for all MOV work among all partners.
IVIR-AC	SAGE noted that a sub-group of IVIR-AC members and external subject experts should make recommendations on the types of prospective studies to assess the non-specific effects of vaccines.	Oct 2014	Ongoing	An ad-hoc consultation on clinical trials for non-specific effects of vaccines (NSE) was held on 16–17 February 2016. Eighteen experts (including 3 IVIR-AC members) contributed to this consultation, whose main objectives were to reach a consensus on priority trial questions and to propose trial designs for each of the priority questions. Protocol synopses for the six different trials that the experts proposed are being prepared for review and discussion at June 2016's IVIR-AC meeting.
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) was 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. Seven proposals have been selected for funding and being implemented with a one year timeline until 2016 A new funding proposal is being prepared for 2016-2017 with support from Gavi and UNICEF.
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 held a meeting May 26-27, 2015, on best practices for JE vaccine effectiveness and impact studies. A draft guidance document will soon be circulated for peer review, followed by publication.

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Japanese encephalitis	Commercial kits for detection of JE-specific IgM should be compared and validated.	Apr 2006	Completed	Assessment using serum was carried out by PATH and published (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 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. 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 3 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 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. 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 bi-regional laboratory training workshop and laboratory network meeting was conducted 17-21 August 2015, at the National Institute of Health in Bangkok, bringing together JE lab staff from both WPR and SEAR. The two-day meeting provided a forum of laboratory experts to update on progress and challenges for the program, the JE laboratory network, the renewal of the roles and responsibilities of the JE network laboratories in the WPR and SEAR, update on new technologies for the diagnosis of JE, and panel discussions on surveillance of JE and possible integration with other non JE causes of Acute Encephalitis Syndrome. The following 3-day laboratory workshop provided hands-on training using the newly introduced InBios diagnostic kits, and compare its performance with other kits used in the two WHO Regions. All laboratories represented used the opportunity to provide updates on the current JE situation with particular focus on laboratory-based surveillance. A bi-regional JE meeting for SEAR and WPR is being planned for 10-14 October 2016.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Lower middle-income countries: sustainable adoption and financing for new vaccines	SAGE requested that WHO facilitate the establishment of a partnership among all relevant stakeholders to consider: pooled procurement; tiered pricing; greater transparency of pricing; and exploring the role that UNICEF, the Pan American Health Organization and foundations can have in assisting these countries with procuring and financing vaccines.	Nov 2010	Ongoing	WHO has set up a MICs Task Force in June 2014. The Task Force includes main immunization stakeholders (WHO, UNICEF, World Bank, GAVI Secretariat, BMGF, AMP, Sabin, Task Force for Global Health) and is working to establish a shared strategy for sustainable access to vaccines in MICs in consultation with countries, 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. The strategy was finalised in April 2015 and presented at SAGE. It was approved to move into implementation phase. Four main areas of action have been identified as the pillars of the MIC strategy: i) Strengthening evidence-based decision-making; ii) Enhancing political commitment and ensuring financial sustainability of immunization programmes; iii) Enhancing demand for and equitable delivery of immunization services; and iv) Improving access to timely and affordable supply. Improving access to timely and affordable supply is seen as the main area where further efforts are needed, especially related to vaccine procurement. This area includes the following activities: increasing procurement skills and knowledge ; increasing access to revolving funds ; harmonizing product choice & registration processes ; increasing availability of price and contract information ; strengthening pooled procurement options and influencing market dynamics (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. Following SAGE's endorsement of the strategy, the WHO Secretariat has led Strategy implementation efforts in collaboration with immunization partners. A first mission was conducted in Swaziland as part of the country engagement process encouraged by SAGE. Also, different small efforts to support countries to strengthen their procurement capacity have taken place. some effort is being undertaken also in the area of decision making and hesitancy. Work on price transparency continues. Despite these efforts, progress in implementation of the strategy is very slow due to lack of funding. As discussed at the April 2015 SAGE meeting, the partners would require US$20M per year to fully implement the strategy.
Malaria	SAGE noted the utility of PPCs to developers and funders, and proposed that the opportunity for input into future PPCs at an early stage for any vaccine of public health importance could be included as part of SAGE’s global public health mandate.	Apr 2013	Ongoing	Malaria Vaccine Preferred Product Characteristics are finalized and available on WHO's website. RSV Preferred Product Characteristics are now under development. In addition, two Ebola vaccine Target Product Profiles have been developed for reactive and prophylactic use, and these are available from WHO's website. A Zika vaccine TPP is now under development and will undergo public consultation in the first half of 2016.

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Malaria Vaccine	SAGE requested continued review of the planning of the pilot implementations and to receive regular updates on the results.	Oct 2015	Ongoing	The WHO position paper was published in January 2016. WHO is working to identify potential funding for the malaria pilots, including discussions with GAVI and UNITAID. No funding commitments have been made. This is a joint two department activity with Global Malaria Programme. A WHO/PATH partnership will oversee the pilots. A public call for expressions of interest (EoI) from Ministries of Health was issued by WHO in December 2015. 10 countries submitted EoI, and WHO is in the process of country selection with the intention to proceed with pilots in 3 countries. The pilots will be cluster randomised with feasibility of implementation, impact and safety as primary considerations. A meeting was held on January 19 with external advisors with the relevant expertise including SAGE, MPAC and GACVS representation. WHO and PATH are preparing a technical proposal, for submission to appropriate financing bodies. The earliest pilots could start in late 2017, with 2018 as a realistic start date if funding can be found. Separate to the pilots there are a set of smaller Phase 4 studies to be sponsored by GSK, with before and after design, and with the primary objective of providing further safety information to meet post-marketing obligations with EMA. WHO and GSK are in discussions to ensure good linkages and complementarity between the GSK sponsored Phase 4 studies and the pilots.
Maternal Immunization	SAGE concluded that the recommending bodies, including WHO, need to engage in a dialogue with regulators and manufacturers to review current regulatory practices against the evidence on risks and benefits and biological plausibility on product safety. SAGE requested WHO to develop a process and a plan to move this agenda forward in support of an increased alignment of data safety evidence, public health needs and regulatory processes.	Nov 2013	Ongoing	WHO is supporting evaluations of product monograph language regarding safety and use during pregnancy, as well as a survey of health care provider's perceptions of the specific product monograph language regarding use in pregnancy. WHO has reviewed various regulatory approaches to labelling of the pregnancy and lactation sections of product inserts, and it has convened several meetings on the subject: a consultation at WHO in July 2014 and a session at a meeting of the Developing Country Vaccine Regulators' Network (DCVRN) in China in November 2014. In collaboration with multiple NRAs globally, WHO has produced a draft guidance document titled 'labelling information of inactivated influenza vaccines for use in pregnant women'. The document is currently available for public comment. It will be revised to reflect the public consultation and reviewed by ECBS in late 2016.
Maternal Immunization	SAGE encouraged the Regional Office for the Americas to document the successful regional experience of delivering influenza vaccine to pregnant women.	Apr 2015	Pending	Regarding PAHO/WHO's documentation of the successful regional experience of delivering influenza vaccines to pregnant women, PAHO has progressed significantly: - we have submitted a manuscript describing influenza uptake in the LAC region since the pandemic, highlighting the improvements in targeting pregnant women for vaccination in 29 countries. -PAHO conducted during 2015, a survey among 14 LAC countries that aimed at describing the process from vaccine introduction decision, to implementation among pregnant women. It also tackled obstacles and enablers in vaccine promotion and uptake. - In order to complement this survey, we are planning another in-depth survey to develop case-studies with key countries that have acquired a lot of experience in maternal immunization. As part of these case-studies countries will share lessons learned. - PAHO convened a multi-disciplinary, inter-institutional working group to develop a field guide for maternal immunization which is in its finalization phase. This field guide targets EPI managers, EPI staff, and other healthcare workers involved in maternal and child health care. it should be published during 2016.
Maternal Immunization	SAGE encouraged WHO to promote more implementation research to generate generalizable data on the best ways to integrate maternal immunization into routine antenatal care in low resource settings	Apr 2015	Ongoing	IVR is in conversations with partners to develop a proposal to conduct maternal immunization implementation research in low-resource settings. IVR is in the process of producing many implementation research tools and guidance regarding: 1) assessment of vaccine confidence/hesitancy in pregnant women; 2) maternal influenza immunization program costing tool; 3) guidance document to estimate the influenza economic burden of a country; 4) guidance document to estimate the cost effectiveness of influenza vaccines in a country; 5) field guide for the evaluation of influenza vaccine effectiveness; 6) maternal immunization AEFI surveillance guidance; and 7) implementation guidance document.

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Measles	SAGE recommended further clinical, immunological, epidemiological and modelling studies regarding the impact of different measles vaccination schedules.	Oct 2015	Ongoing	The RIVM in the Netherlands (the same group that did the systematic review of use of measles vaccine under 9 months of age) will have results from their clinical studies of the immune response to an early dose of MMR vaccine by end 2016. Modeling work is ongoing at US CDC to explore the effect of different vaccination schedules on the epidemiology of measles. An update on this work will be provided to the SAGE MR Working Group during the course of 2016.
Measles	SAGE requested evidence on the need for measles revaccination of HIV-infected adolescents and adults. Further research is needed to monitor the long-term immune responses to measles vaccine in HIV-infected children revaccinated after starting HAART and in HIV-infected children starting HAART prior to receiving their first dose of MCV.	Oct 2015	Ongoing	Compiling the evidence on the need for measles revaccination of HIV-infected adolescents and adults is on the 2016 work plan of the SAGE Measles and Rubella Working Group (SAGE MR WG). Professor William Moss at Johns Hopkins University is taking the lead on this work. Research on the long-term immune responses to measles vaccine in HIV-infected children revaccinated after starting HAART needs to be taken up by clinical research groups and is not the focus of the SAGE MR WG.
Meeting preparation	SAGE members asked that in the executive summaries inserted in the Yellow Book for each section, an orientation be included describing the entire package of documents inserted.	Apr 2015	Ongoing	This has been specifically flagged and requested from each WHO session focal point in preparation for the October 2015 SAGE meeting. The same applies to the upcoming SAGE meeting in April 2016 where focal points will be asked to provide an executive summary as necessary.
Meningococcal A conjugate vaccine	SAGE recommended that countries completing mass vaccination campaigns introduce meningococcal A conjugate vaccine into the routine childhood immunization programme within 1–5 years following campaign completion, along with a one-time catch-up campaign for birth cohorts born since the initial mass vaccination and which would not be within the age range targeted by the routine immunization programme.	Oct 2014	Ongoing	The recommendations from SAGE are reflected in an update to the WHO meningococcal vaccine position paper. The updated guidance has been published in the Weekly Epidemiological Record WER on 20 February 2015: http://www.who.int/wer/2015/wer9008/en/. Eight of the 26 meningitis belt countries have already submitted an application to Gavi, the Vaccine Alliance in January 2015 (Ghana), in September 2015 (Burkina Faso, Central African Republic, Chad, Mali, Sudan) and in January 2016 (Niger, Nigeria) for introduction of the meningococcal A conjugate vaccine into their routine immunization programme, with a single dose at 9, 15 or 18 months of age concomitantly with the administration of the first or second dose of Measles/Rubella vaccine. Another 7 to 8 meningitis belt countries intend to apply for the introduction of the vaccine into their routine programme at the next couple of Gavi application windows in May and in September 2016. The first introductions of the vaccine into routine programmes are expected to occur in 2016.
Middle Income Countries Strategy	SAGE called upon WHO Secretariat to report back on progress in implementation of the Middle Income Strategy.	Apr 2015	Pending	WHO will work on the implementation of the MIC strategy and will report back to SAGE in October 2016.
Multiple injections	SAGE noted the need for further research on multiple injections during the same visit and recommended the following research topics and activities: (i) impact of multiple injections in the same visit on vaccine coverage, disease reduction, vaccine programme success and caregiver and provider experience; (ii) development of a standardized monitoring protocol for acceptance and acceptability by caregivers and providers and for prevalence of adverse events; (iii) development of optimal provider and infant caregiver communication approaches; (iv) optimal multiple injection administration techniques, and (v) development of new technologies, such as intradermal patches and new combination vaccines, which would decrease the number of vaccine injections in a single visit.	Apr 2015	Ongoing	A multiple injection study is about to be conducted in Nepal in collaboration with US CDC to evaluate healthcare provider and infant caregiver attitudes and practices regarding administration of multiple injectable vaccines in the same visit following introduction of IPV and PCV. A separate work stream in WHO IVB - in conjunction with WHO EMP and external partners (PATH, AMP)- is investigating the development of microarray patch technologies with IPV and MR with special emphasis on Preferred Product Characteristics and relevant regulatory pathways.

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Pain mitigation	SAGE recommends that WHO: 1) includes pain mitigation recommendations with WHO immunization practice guidance materials; 2) disseminates pain/distress mitigation recommendations through the usual dissemination channels, immunization managers, National Immunization Technical Advisory Group (NITAG) and partner organizations; 3) monitors and evaluates the implementation success of pain mitigation measures; 4) works with industry, ECBS and regulatory agencies to advocate that grading of pain experienced during the vaccine injection be included in data for licensing and in the product monograph.	Apr 2015	Ongoing	Internal discussions have taken place on how to move forward across relevant WHO departments. A brief position paper was drafted based on the SAGE recommendations and published in the Weekly Epidemiological Record on 25 September 2015. This formed the basis for additional proactive communication activities. As example of actions in response to points 1 and 2 WHO endured that information in WHO guidance on multiple injections and IPV was consistent with the SAGE recommendations on reducing pain, specifically in two documents: Practical considerations for the successful introduction of IPV, and Multiple Injections: Acceptability and Safety, both available on this web page. The PP on reducing pain was also added on the same web page. In relation to the training aspects for IPV introduction, we updated training modules for health workers, also to reflect the recommendations from the latest PP. The Immunization in Practice recently published has in module 5 'Managing immunization sessions', recommendations on vaccine sequence (increasing pain- oral before injection, rota before OPV), positioning the recipient, no aspiration etc. IIP will be widely distributed to countries and the last edition was also translated into several local languages. Work is also ongoing to ensure appropriate incorporation of pain mitigation in WHO guidance documents when they get updated and to ensure that any recommendation posted on the web that would be at odd with SAGE's guidance would be adjusted/removed. The pain mitigation guidance has been included in the NITAG resource center. PDVAC will consider pain mitigation within their preferred product characteristics to guide target product profiles and include the topic in their envisage Vaccine special issue on the PDVAC pipeline analyses for 25 pathogens. More specific activities still need to be implemented with respect to points 3 and 4.
Polio	SAGE advised GPEI to develop a targeted advocacy and communication plan to engage key countries and stakeholders to ensure completion of phase I and implementation of phase II, including establishment of national containment authority and national regulation for containment of poliovirus in designated essential poliovirus facilities.	Oct 2015	Ongoing	A communications plan and a new web page for poliovirus containment have been developed. A map showing global progress with completion of phase I of GAPIII is posted every week. The map also identifies countries that have desgnated poliovirus-essential facilities and have nominated national authorities for containment that will certify facilities against GAPIII.
Polio	SAGE recommended working closely with countries on activities towards type 2 oral polio vaccine (OPV2) withdrawal.	Apr 2013	Ongoing	In January 2014 a joint letter to all oral polio vaccine (OPV)-only using countries was sent by the WHO Director General and UNICEF Executive Director, and the 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. This was followed up in May 2015 with a joint letter from the DG and UNICEF ED to all tOPV using countries on the importance of planning for the switch. All regions have held, at least one meeting that included a substantive focus on IPV introduction in 2014/5 and have held or will hold the same on the tOPV to bOPV switch in 2015. 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 for IPV and the switch. Work is now ongoing to i) ensure that declared intent materializes into commitment and ii) countries with no plan developed for the switch have one ready before the end of the year. In alignment with the SAGE April meeting discussions and the WHO resolution on the Switch, technical materials and standard operating procedures (SOPs) have been developed to accelerate switch planning at country level and have been shared with countries through regional consultations. Planning for the Switch has continued in an accelerated manner with substantial technical assistance provided to countries through Partners and Regional offices. Financing is also be provided to high risk countries. A full update will be provided to SAGE in April as the Switch will be taking place at about that time. A special tracking effort has been undertaken to ensure that no country falls between the cracks and is entirely ready for the Switch. As of January 2016 only a handful of countries are of concern and the topic of specific attention by WHO and UNICEF.

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Polio	SAGE emphasised that UNICEF Supply Division, PAHO Revolving Fund and WHO should secure the global supply of prequalified bOPV.	Oct 2015	Ongoing	OPV supply is considered sufficient to meet requirements at the moment both for tOPV through to the switch as well as for bOPV to ensure timely introductions in routine programmes of this vaccine after the switch for countries procuring through UNICEF. The additional award made for 70 mds tOPV has allowed Pakistan to adjust its plans and to add more tOPV to the calendar and ensured sufficient supply to meet VDPV2 outbreaks in Myanmar and Lao. Countries procuring through UNICEF are on track for procurement of bOPV to introduce in routine programmes after the Switch, and expect to have continued sufficient bOPV supply beyond the switch. Demand forecasts are under review with the Vaccine Supply Task Team to ensure sufficient OPV supply will be available for 2017 and beyond.
Polio	SAGE advised the GPEI to ensure a full outbreak response to interrupt the cVDPV2 outbreak in Guinea and in South Sudan within 120 days of outbreak confirmation.	Oct 2015	Ongoing	South Sudan: the country reported 2 cVDPV2 cases in 2014 and one aVDPV2 on 16th of April 2015. Three mop up rounds were completed in Unity State after 2014 cases (age 0-15 years); 4 NIDs were completed in 2015 in the seven secure states and two were conducted in Unity, Jonglei and Upper Nile States. Due to persisting insecurity in these three states many areas remain unvaccinated. Four additional WHO international consultants are being deployed to South Sudan in addition to nine international WHO consultants who are in the country to support polio operations. CDC is in the process of deploying 25 international STOP team members. Guinea: An outbreak response was launched in the eastern part of the country during the week of 14 September covering 4 regions with 20 (52.6%) districts of the country. Two additional rounds (one regional and one national) were conducted in November and December. The quality of December SIA round was good in most of the locations, including the infected Kankan region, although the two preceding rounds had been assessed as falling short of the required quality standards to stop transmission. Three additional SIA rounds are planned in the country before the Switch. The surge is almost complete with 8 international and 38 national consultants deployed to support outbreak response and outbreak coordinator in place. AFP case reporting has improved in 5 of 8 Regions and active surveillance commenced recently. The initial issues with shipment of samples for laboratory investigation were resolved; currently the samples are shipped to Institute Pasteur in Dakar.
Polio	The documentation for 'legacy planning' should include contributions from communities and front-line health workers on their experiences with the polio programme, what it has meant for them and how lessons learnt could further improve the routine vaccine and health programme.	Apr 2013	Ongoing	Capturing this information is fully integrated into the country-level transition planning guidelines, and the work of Legacy Management Group of the Global Polio Eradication Initiative is emphasising the importance of this.

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Polio	Sufficient capacity should be established at the global level to provide technical and programmatic support to countries to plan and implement all activities associated with type 2 oral polio vaccine (OPV2) withdrawal and introduction of inactivated polio vaccine (IPV).	Apr 2013	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. All of the expected GAVI eligible countries (71) have applied and been approved for IPV introduction support. For non GAVI countries, a financing mechanism has been rolled out to support 16 countries in Tier 2 and Tier 3 or LMIC (low and middle income countries) which are 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. 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. To date, 92 countries introduced IPV since January 2013, including all 17 tier 1 countries and 14/19 tier 2 countries. Due to the IPV supply shortage, 20 low-risk countries and one self-procuring country (Indonesia) will introduce IPV after the switch. The effort is now focusing on managing the IPV supply and 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.
Polio	SAGE encouraged further engagement of WHO regional offices in regard to the polio legacy planningto ensure adequate technical support to countries.	Oct 2015	Ongoing	Work has been ongoing on this front. A Legacy discussion took place at the regional Committee meeting of AFRO in October and a Legacy Working Group has been established by the AFRO Regional Director. Planning guidance is now available for countries and the GPEI Legacy Management group, which includes representations from EPI and Gavi, among others, is actively engaged in supporting the planning process. Funding has been made available by the GPEI to secure Technical Assistance to 14 countries for Legacy planning purposes.
Polio	SAGE requested its Polio Working Group to provide urgent guidance on optimal management of IPV supply and mitigation of other risks in case the IPV supply is further reduced.	Oct 2015	Ongoing	IPV supply situation is closely monitored. In February and March 2016, the two main IPV suppliers (i.e. Bilthoven Biologicals and Sanofi Pasteur) informed WHO/UNICEF that they will substantially reduce or delay the quantities of IPV supplied in 2016 and 2017, due to technical challenges in scaling up IPV bulk production and the associated quality control testing and releases. This has created significant delays in IPV introduction and shortages of supply in many countries. SAGE WG and SAGE reviewed the IPV supply situation closely, and issued a statement (please see separate document).
Polio	SAGE advised GPEI to accelerate implementation of the WHO Global Action Plan for containment (GAPIII) including: a) all countries completing phase I; b) regional focal points closely monitoring country activities and ensuring each country completes its inventories of facilities that hold or handle polioviruses, and destroys or commits to destroying WPV2 by end 2015 and any other type 2 containing materials including Sabin poliovirus by July 2016.	Oct 2015	Ongoing	As of 8 March 2016, 134 countries have completed the first part of Phase I, with 38 Member States having yet to respond and 22 Member States yet to complete their reports on the destruction or planned retention of WPV2 or VDPV2 materials. By end July 2016, 3 months after the switch, countries are expected to complete the second and last part of Phase I, and report on the destruction or planned retention of all Sabin type 2 poliovirus materials.

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Polio eradication	SAGE requested the polio Working Group to continue monitoring progress towards cVDPV2 elimination and ensuring that remaining challenges are addressed including contingencies for vaccine supplies (IPV, bOPV and tOPV), registration of bOPV for routine use, surveillance sensitivity, and reaching inaccessible children.	Apr 2015	Ongoing	The Polio Working Group reported to SAGE in October 2015 and SAGE reconfirmed April 2016 as the definite date for OPV2 withdrawal.
Polio eradication	SAGE noted the importance of the work on the polio legacy and asked for a full report on this at its October 2015 meeting.	Apr 2015	Completed	This was discussed during the September 2015 Working Group meeting and presented to SAGE during the October 2015 meeting.
Regulatory	SAGE recommended that the further development of the Emergency Use Assessment and Listing procedure being developed by WHO, which would allow use of a vaccine in the context of a Public Health Emergency of International Concern, be done in close consultation with relevant regulatory authorities, including those of the affected countries.	Apr 2015	Ongoing	A document entitled “Vaccine evaluation in public health emergencies – review of regulatory pathways in selected countries” was prepared and briefly presented to SAGE WG on Ebola vaccines in August 2015. In October 2015, the document was submitted to the Expert Committee on Biological Standardization (ECBS) for review and advice. The Committee considered that a guidance document might be of value to NRAs and other public health organizations, however it also recognized the complexity of emergency situations each of which is essentially unique, and that decisions ultimately rest on a benefit/risk assessment. The ECBS agreed that the report could provide useful information to NRAs, and looked forward to reviewing progress in 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 health economists with experience in vaccine implementation research. Recruitment of new members is ongoing. There was a call for new members in 2015. Three potential candidates were selected to attend the June 2015 meeting. The mathematical modeler was selected to become a member but the two health economists were not selected as they did not meet the expectations. A new call for Committee Members will be issued in Q1-Q2/2016.
Reports from other advisory committees on immunization	WHO and NIBSC should develop with other stakeholders, a business plan to assure long-term security of the development of WHO reference preparations as a global public health resource and additional efforts should be undertaken to disseminate outcomes of the committees deliberations and to explain the relevance of its work to the broader immunization community.	Nov 2006	Pending	A comprehensive review of the work of the Expert Committee on Biological Standardization (ECBS) is ongoing. The review will include (but not be restricted to) consideration of communication of ECBS outcomes. Discussion on a paper on the process of the review was initiated by ECBS during its October 2014 meeting; however biotherapeutic biological drugs were identified as first priority.
Smallpox vaccines	SAGE recommended that WHO initiate discussions with countries in possession of smallpox vaccine to establish mechanisms for replenishment of the WHO stockpile in case of need.	Nov 2013	Ongoing	Discussion with the French Government for the donation of 5 million doses and Japanese Gov for 10.000 doses are still ongoing. WHO is working on smallpox vaccine prequalification for the emergency stockpile. A WHO meeting took place in Geneva 7-8 September 2015 to discuss with the National Regulatory Authorities and vaccine manufacturers what would be the minimum criteria to pre-qualify smallpox vaccines in case of re-emergence of variola virus. The report will be pusblished in April 2016

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Surveillance	SAGE endorsed the recommendations of the ad hoc TAG for improving the quality of the IB-VPD surveillance network and urged that the objectives of this network be more clearly defined, that collaboration with other surveillance systems and laboratory networks (i.e. the polio/measles laboratory networks) be continued, and that, where feasible, activities be linked with other programmes enhancing country capacity, including implementation of the International Health Regulations. SAGE urged greater attention to integration of data systems, which would facilitate real-time analysis and performance monitoring. SAGE also noted the opportunities for integration by building upon the enhanced capacity developed by these networks to conduct surveillance for other diseases using a similar case-definition and personnel trained in applying and adhering to rigorous surveillance protocols. Both networks should continue to share experiences with the polio surveillance network. Integration efforts must be strategically designed in ways that are logical and synergistic.	Nov 2013	Ongoing	During 2013, a global strategic review was conducted of the invasive bacterial vaccine preventable diseases (IB-VPD) and rotavirus sentinel hospital surveillance networks. During that meeting, 50 recommendations were made to advance the status of both networks. During 2014 and 2015, significant progress was made to further improve the IB-VPD and rotavirus sentinel hospital surveillance networks and additional recommendations made. 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; by 2015, all six WHO regions were reporting case-based data linked to laboratory testing. Data management processes continue to be improved toward a more systematic approach in reporting, cleaning, analysing and interpreting data. The reference laboratories are appropriately supporting sites and network laboratory performance has been successfully monitored by the global external quality assessment program as well as quality control programmes. Sentinel site and laboratory assessments are ongoing at priority sites. The most recent data available is from 2015, and it reflects the strength of the data and the network. One recent global analysis of IB-VPD data found that PCR identified 5-7 fold more bacterial meningitis than culture depending on region and CSF characterization and that in resource-limited settings, targeted PCR testing of probable bacterial meningitis cases only may maximize efficiency. Based in part of this analysis, the recommendation that all IB-VPD cerebrospinal fluid specimens should be tested by PCR at an RRL has been implemented. Network data has contributed to vaccine introduction decisions, such as choice of Pneumococcal Conjugate Vaccine (PCV) formulation, and the surveillance networks have been used as platforms for vaccine impact evaluations, particularly for Rotavirus Vaccines (RV). Moving forward, the rapid introduction of PCV and RV by Member States now requires the surveillance networks to focus on improving baseline data for sites in non-vaccine using Member States and to ensure consistent surveillance practices for sites that meet inclusion criteria in vaccine-using Member States. A web-based data management tool is still under development and has great potential to improve data quality and sharing. Some new activities revolve around testing for other pathogens and integrating with other VPD surveillance platforms. Specifically, a pilot to include typhoid surveillance as part of IB-VPD surveillance is being implemented in 2016 in 2 sites in Asia and 2 in Africa. We are discussing how to better integrate IB-VPD meningitis surveillance with existing meningococcal meningitis surveillance systems. We are exploring how to use the rotavirus surveillance network to monitor norovirus, and a network study is using the TAC technology to test for other enteric pathogens in specimens collected as part of the network. WHO, the informal Technical Advisory Group and partners will work to implement recommendations to further improve the network during 2016 including to strengthen programme management. Other activities planned include:an evaluation of the cost of surveillance to help countries and funders develop sustainable surveillance plans; strengthening involvement of Ministry of Health and national EPI programmes; defining a subset of sites where PCV and/or RV vaccine impact evaluations may be feasible due to sufficient pre- and post-vaccine introduction data; draft guidelines for rotavirus data analysis/interpretation and standard operating procedures; re-evaluate site inclusion criteria: for rotavirus, reduce the number of annual stool specimens needed in vaccine using countries; for IB-VPD, include consistently performing sites that enroll 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	Progress in TB vaccine development was reviewed by PDVAC in September 2015. Modelling studies suggest, and consensus is emerging that targeting the adolescent/adult population, who carry the heaviest disease burden, will have the highest and most immediate public health impact due to reduction in transmission. Key data points will emerge from separate clinical studies with 3 candidates (H4, VPM1002 and M.Vaccae) during in 2016. M.vaccae is a heat killed homogenized lysate being developed by Anhui Zhifei Longcom, China, undergoing Phase III testing for prevention of pulmonary TB in latently infected adults in China. VPM 1002 is a recombinant BCG, originally developed by the Max Planck Institute; now licensed to the Serum Institute of India (SII), Pune, India and being developed with Vakzine Projekt Management (VPM), Hannover, Germany, currently in Phase II trial vs. BCG in HIV+ and HIV- infants <12 days old (South Africa), interim data assessment anticipated in mid 2016. H4/IC31 is an adjuvanted recombinant protein under development by sanofi Pasteur, SSI and Aeras, currently in a Phase II prevention of infection study in adolescents (Phase II) with data expected in Q3 2016. WHO is planning to meet with GSK and VPM/SII to discuss their programs in May 2016.
Typhoid	Establish a SAGE working group on typhoid conjugate vaccines in 2016 to prepare for a SAGE review of the evidence in 2017.	Oct 2015	Ongoing	The SAGE Working Group on Typhoid Vaccines was established in March 2016. The Working Group will review updated evidence to support the use of typhoid vaccines overall with a focus on typhoid conjugate vaccines. A SAGE review is tentatively scheduled for Oct 2017.
Un/under-immunized children	SAGE requested that WHO quickly roll out tools so that other countries can address low coverage of vaccination.	Nov 2010	Ongoing	The in-depth tool "A Guide to Tailoring Immunization Programmes (TIP) has already been developed and used by WHO-EURO (European Regional office). Currently the Univ. of Witwatersrand in South Africa has been contracted to adapt the methodology to developing countries, and less intensive consultant-based inputs. The Health Worker KAP tool has been completed and will be piloted with the assistance of JSI in Kenya. Work is ongoing on the tool to assess "Missed Opportunities". On a broader level, a companion document to the GVAP focusing on Routine Immunization, entitled "Global Routine Immunization Strategies and Practices" (GRISP) is in the final stage of drafting, and has been presented to the SAGE WG on DoV twice. In addition to a comprehensive framework of RI strategies, it highlights nine "transformative investments" to guide global partners and countries in RI strengthening.
Vaccination during humanitarian emergencies	SAGE emphasized the need to advance work on refining guidance in delivering continuous immunization services during humanitarian conflicts. A session on human emergencies will tentatively be slotted at the April 2016 SAGE meeting.	Oct 2015	Ongoing	A WHO meeting on implementation of vaccination during humanitarian emergency situations was convened in Cairo from 12-14 January 2016.The objectives were to: -reflect on the experience of EMR countries in implementing vaccination in humanitarian emergencies and the issues, challenges, best approaches and existing country guidance documents to ensure satisfactory vaccination of the target populations. -reflect on countries experience using Vaccination in acute humanitarian emergencies: a framework for decision making -build on countries experience to initiate development of a draft guidance document on the implementation of vaccination in humanitarian emergency situations. A draft version of the guidance document on implementation issues has been produced by EMRO that will undergo broader consultation before finalization. Further there will be adjusting/updating of the framework based on the feedback received during the meeting as well as further development of an operational manual of the framework based and web based interactive tools to support its use and facilitate further updating. Attempts will be made to have a proactive dissemination and communication plan to ensure adequate distribution. Although there will not be a separet SAGE session in April 2016 this will be featured in the IVB Director's global report at this meeting.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Vaccination during humanitarian emergencies	SAGE also suggested that the framework approach to vaccine decision-making could be considered for other health interventions in emergencies.	Apr 2012	Ongoing	A discussion was held at the MICs Task Force meeting held in February 2015 on the possibilities of having an emergency fund for vaccines in disaster situations. The discussion resulted in a mapping of emergency funds available and gaps, which was presented in the April SAGE meeting in 2015. No further updates have resulted from this discussion. The Emergency Risk Management and Humanitarian Response (ERM) Department is currently undergoing a reform process. Once the process is finalized we will have a clearer indication of our engagement in and collaboration with this area of work.
Vaccine coverage	WHO to identify appropriate methods and develop guidelines for collecting, analysing, and interpreting biomarkers for validating coverage.	Nov 2011	Ongoing	Currently, WHO is developing global guidelines on conducting serosurvey studies on measles and rubella and primarily to be applicable in a pre- and post-SIA (supplementary immunisation activity) setting. An expert working group has been assembled and based on the expertise in the various fields of each of the members, needed to conduct such studies, including statisticians, epidemiologists, laboratory experts, and program experts, given subtasks in developing parts of these guidelines that pertain to their respective expertise. A working draft has been circulated for comments and will be finished by the end of 2015 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 2016 and will run during the entire year of 2016. Based on the outcome, the working draft guidelines will be corrected where needed and finalised. The final document is planned to be ready by end of 2016 and to be rolled out as a tool to evaluate the immune status of the target or targeted population.
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. The working draft of the manual has been distributed and posted on the departmental web site(http://www.who.int/entity/immunization/monitoring_surveillance/Vaccination_coverage_cluster_survey.pdf?ua=1). A briefing workshop on the methodology for regional focal points and consultants has been conducted in December 2015.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
Vaccine coverage	SAGE recommended that WHO support new research for biological specimen collection including rapid on-site diagnostics that could improve coverage and susceptibility estimates. Improved serological surveillance techniques could be integrated with existing population-based surveys such as DHS or MICS. These research topics should be included on the QUIVER (now IVIR-AC) agenda.	Nov 2011	Ongoing	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 detailed plans for future commercialization possibilities.
Vaccine delivery research	SAGE requested that IVIR-AC explore research studies and methods including behavioural science studies for ranking reasons behind lack of vaccine delivery and other 'barriers to access'.	Oct 2015	Ongoing	IVIR-AC reviews methods and encourages studies on vaccine delivery costing and financing (HPV, influenza and OCV) and vaccine uptake/hesitancy.
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 initiated on how to advance the establishment of a network of expertise/excellence and collaborating centres by capitalizing on currently ongoing initiatives and activities which have been established and are conducted by WHO (HQ and Regions), partners and stakeholders in the field of vaccine hesitancy. Resources to support related activities are currently being established at HQ and in EURO. A package listing resources from a number of support centers which could assist countries and regions has been prepared and was circulated to regions in December 2015.
Vaccine Hesitancy	SAGE underlined the importance of distributing the matrix of determinants, the definition of hesitancy and the other deliverables to countries and partners.	Oct 2014	Ongoing	Discussions and presentations were held in the context of the immunization managers' meeting in the Eastern Mediterranean Region (EMR) and the African Region (AFR) Task force on immunization(TFI) meetings in 2014 and 2015. A Special Issue on Vaccine Hesitancy has been published in August 2015 in the journal Vaccine with a series of 10 full papers plus one editorial. In conjunction, a WHO press briefing was held on 18 August 2015 to emphasize WHO initiatives addressing vaccine hesitancy. This generated much positive media coverage. A compilation of centers to assist countries in addressing vaccine hesitancy has been finalized and sent to WHO regions to disseminate to countries. A manuscript has been submitted which outlines the results of the 2015 JRF indicators on vaccine hesitancy. The manuscript contains the matrix of determinants and the definition of vaccine hesitancy.
Vaccine Hesitancy	SAGE encourages validation of the developed compendium of survey questions on vaccine hesitancy, which have been assessed and validated only in some high-income countries or not at all.	Oct 2014	Ongoing	Discussions with various stakeholders are ongoing (Centre for Disease Control CDC, WHO EURO, Middle Income Countries MIC task force) on the ways forward to identify partners to take on the validation of the survey quesions. The MIC task force framework was presented to SAGE during the April 2014 meeting, which highlighted the importance to advance this initiative. Currently it is being explored how to secure funding from donors in support of the listed activities and advance validation of the questions in LMIC settings.

Topic	Recommendations/Action item	Meeting Date	Status	Comments and Follow up
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 pregnancy has been made available to SAGE in November 2013 and is now available on the Global Vaccine Safety (GVS) website. A new work track was started with WHO Initiative for Vaccine Research (IVR) in order to harmonize safety monitoring during pregnancy clinical trials. WHO is a contributor to the Gates funded Global alignment of immunization safety assessment in pregnancy project that should run until the end of 2016. WHO is also advising another Gates funded project with Seattle Children's hospital on maternal immunization pharmacovigilance in low- and middle-income countries.
Vaccine Supply	SAGE requested WHO to produce a report on the security of the supply of affordable vaccines and encouraged donors to invest in the development of new vaccine technologies that facilitate the delivery of effective, affordable vaccines to populations most at risk.	Nov 2012	Ongoing	Concerns about the ongoing shortages of traditional vaccines persist. Internal WHO discussions are in progress, in particular in context of WHA resolution 68.6, as well as discussions with partners. WHO secretariat (EPI) is now working to develop an approach to expand timely access to supply for both traditional and new vaccines through improved demand and supply management/forecasting. A report on this area of work will be provided to SAGE in October 2016. A session on preempting vaccine shortages will be organized for SAGE April 2016.
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.The amendment will enter into force and be legally binding upon all IHR States Parties on 11 July 2016. There were no legal rejections or reservations expressed by countries. 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 travelers. As of 2 February 2016, 49 countries or territories have notified WHO that already accepted the validity yellow fever (YF) vaccination certificate for life (see http://www.who.int/ith/2016-ith-annex1.pdf?ua=1.)

Immunization Highlights 2015:
Select WHO's achievements in vaccines and immunization

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Acknowledgements

This document was written by Dr Robin Biellik, an independent consultant, for the Department of Immunization, Vaccines and Biologicals at the World Health Organization, Geneva.

The Department of Immunization, Vaccines and Biologicals thanks the donors whose unspecified financial support has made the production of this document possible.

Foreword

There is arguably no single preventive health intervention more cost-effective than immunization. Time and again, the international community has endorsed the value of vaccines and immunization to prevent and control a large number of infectious diseases and, increasingly, several chronic diseases that are caused by infectious agents. Today, parents, communities and governments have the responsibility to strive for universal coverage with vaccines that have the potential to bring about the elimination of diseases that have limited human development for millennia.

The year 2015 was significant for global immunization, marking the mid-point in the 2011-2020 Global Vaccine Action Plan (GVAP). The current status of each of GVAP's main targets was evaluated by the WHO Strategic Advisory Group on Immunization. Results showed that several important targets remained off-track and at risk of not being met in full by the end of the decade.

In response, WHO's Vision and Mission in Immunization was developed to create a unifying vision on immunization across all departments and levels and thus to enable WHO to anticipate and respond more effectively to opportunities and challenges in future.
In 2015, WHO continued to provide leadership in setting immunization policy and, working in close collaboration with Ministries of Health, partner and funding agencies, and community organizations worldwide, has overseen the successful implementation of those policies from global to household level.

This report highlights a number of specific achievements during 2015 of the WHO team based in its headquarters in Geneva. It highlights areas of notable progress that will be consolidated and built upon going forward, while renewed effort and investment are needed in order to ensure that all of GVAP's targets are met in full and on time in countries.

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1. Setting immunization policy

1.1. Publication of a journal special issue on vaccine hesitancy.

The increasing frequency of reports on vaccine hesitancy from countries regardless of their level of development highlights the gap between expert consensus and concern among the general public about vaccine safety and effectiveness. Safety was perceived as the main driver of hesitancy and the WHO Strategic Advisory Group of Experts on Immunization (SAGE) noted that increasing publicity in industrialized countries could spread globally and delay progress towards the achievement of the Global Vaccine Action Plan goals. No clear definition and scope of the problem had been established and proven strategies to address vaccine hesitancy were lacking.

In 2012, this led WHO to establish a SAGE Working Group of international experts covering a wide range of expertise in order to conduct a systematic review of the drivers and impact of vaccine hesitancy and strategies that could be used to mitigate its impact. This work was presented to SAGE in 2014.

A series of ten publications, compiled in the Special Issue on Vaccine Hesitancy published in Vaccine journal, further expands on the SAGE report and presents SAGE's huge body of work to define and address vaccine hesitancy[1]. Drawing on examples from around the world, the papers included in the Special Issue demonstrate that vaccine hesitancy is complex, and the reasons for delaying or refusing vaccination are highly variable and context-specific. Vaccine safety is only one of the many potential drivers of hesitancy!

The Special Issue proposes standard survey questions for measuring vaccine hesitancy and its determinants globally and at national/subnational level. It includes a systematic review of the literature on strategies to address the problem. The series of publications concludes with a set of recommendations on the way forward targeted at WHO, partner agencies, regional and national technical advisory groups on immunization, national governments and civil society organizations. This guidance been very positively received by immunization managers. A network of support centres to assist countries in dealing with hesitancy has been developed.

The release of the Special Issue triggered international media interest highlighting the positive perception by the general public as well as the scientific community of the role that WHO took on this topic as a public health problem to highlight and address.

[1] http://www.sciencedirect.com/science/journal/0264410X/33/34

1.2. Publication of a WHO position paper on pain mitigation.

Fear of injection, due to pain, during immunization is one of many factors that lead some individuals to delay or refuse vaccinations. Studies show that pain at the time of vaccination is a primary source of anxiety for caregivers of children. Concerns over vaccine safety and mistrust in the health care system are also factors leading to vaccine hesitancy and lower vaccination coverage.

The WHO Strategic Advisory Group of Experts (SAGE) on Immunization studied the feasibility of adapting Canada's current clinical practice guidelines for reducing pain and fear from vaccine injections for global implementation. Based on SAGE's thorough review of the evidence and subsequent generation of recommendations, WHO published its first position paper on reducing pain at the time of vaccination[2]. WHO recommends practical and inexpensive measures that can be applied by national immunization programmes in all countries regardless of their level of development and across all age groups. The guidance makes the following points:

- Health-care personnel administering vaccinations should remain calm, collaborative and well informed, and use neutral words when administering the vaccine such as "here we go" instead of "here comes the sting."
- Recipients of the vaccines should be positioned properly, according to age. Infants and young children should be held firmly by their caregiver. Older individuals should sit upright.
- If the cultural context permits, infants should be breastfed shortly before or at the time on immunization.
- Aspiration or pulling back of the plunger of a syringe prior to intramuscular injections should be avoided as this may increase pain.
- When multiple injections are scheduled to be administered in the same vaccination session, they should be given in reverse order of painfulness – ending with the most painful.

When caregivers are made aware of what they can do to comfort their child before and during vaccinations, hesitancy can be effectively reduced. Reducing pain is considered good practice for immunization programmes worldwide. Implementing WHO recommendations can contribute to achieving and sustaining high vaccine coverage and increasing child survival rates.

[2] http://www.who.int/immunization/policy/position_papers/reducing_pain_vaccination/en/

1.3. Recommendations on the use of the first malaria vaccines.

After a development process lasting over 25 years, the world's first malaria vaccine received a positive regulatory assessment by the European Medicines Agency in 2015. WHO developed a novel process to enable joint decision-making by committees from two programmes: the Malaria Policy Advisory Committee (MPAC) of the Global Malaria Programme and the Strategic Advisory Group of Experts (SAGE) on Immunization. SAGE and MPAC met in a Joint decision session and recommended that subnational pilot studies of RTS,S/AS01 malaria vaccine under field conditions should be implemented in 3-5 sub-Saharan African countries to answer remaining questions mainly concerning the programmatic feasibility of vaccine roll-out, plus further issues on vaccine safety and impact. It will be important to evaluate the field implementation of the vaccine in routine health systems particularly in view of the need for a four-dose schedule that requires new immunization contacts. The schedule is a three-dose initial series given between 5 and 9 months of age, followed by a fourth dose at 15–18 months after the third dose.

By December 2015 WHO had launched a call for expressions of interest from Ministries of Health in sub-Saharan African countries. There was a strong response to the call, indicating great interest from countries in taking part in the pilots. The earliest start date for the pilots is late 2017.

This is a critical step for the first malaria vaccine, and the outcomes will play a large role in future product development using the public-private partnership approach for indications restricted to low income settings. WHO and PATH are now working to establish a partnership in order to implement the next steps of the pilot implementation programme, with some analogies to the WHO-PATH partnership for the development of meningococcal type A vaccine. Additional information on programmatic feasibility, safety and impact will be generated that will allow SAGE and MPAC potentially to broaden their joint recommendations on vaccine on a larger scale.

1.4. Synchronization of the global switch from trivalent to bivalent oral polio vaccine.

Withdrawing the type 2 component of oral polio vaccine (OPV) is a crucial part of the Poliomyelitis Eradication and Endgame Strategic Plan, in order to eliminate very rare cases of vaccine-associated paralytic polio (VAPP) or circulating vaccine-derived polioviruses (cVDPVs). The type 2 vaccine virus accounts for 40% of VAPP cases and upwards of 90% of cVDPV cases. However, the wild type 2 virus has not been detected since 1999 and in September 2015 was declared to have been eradicated.

In October 2015, the Strategic Advisory Group of Experts on immunization (SAGE) confirmed that the synchronized global withdrawal of the type 2 component of the oral poliovirus vaccine (OPV) should occur in April 2016, in a two-week window from 17 April to 1 May 2016. The coordinated switch from trivalent to bivalent OPV constitutes a major milestone towards polio eradication.

As part of a review of type 2 vaccine-derived poliovirus epidemiology and all readiness criteria for the switch, SAGE concluded that significant progress had been made since its last meeting in April 2015.

SAGE's landmark decision follows the endorsement by the World Health Assembly in May 2015, when Ministers of Health from 194 member states adopted a resolution on the final steps required to eradicate polio, paving the way for a world free of polio. As a result of these steps, all countries and partner agencies were advised to make all necessary preparations for April 2016 for the coordinated global withdrawal of OPV type 2.

WHO has developed and disseminated a full set of guidance materials to support planning and implementation of the switch, including templates and tools for planning, logistics, communications, training and monitoring[3].

1.5. Publication of an updated WHO position paper on pertussis vaccines.

Pertussis, commonly known as whooping cough, is a highly contagious respiratory disease known for characteristic, uncontrollable, violent coughing. Pertussis affects individuals of all ages, but can be deadly for infants. The disease continues to be a public health concern despite high vaccination coverage.

The main aim of pertussis vaccination is to reduce the risk of severe pertussis in infants. Therefore, the ongoing priority of immunization programmes worldwide is to vaccinate at least 90% of infants with three doses of high-quality pertussis vaccine starting at six weeks of age. Reasons for the recent resurgence of pertussis observed in a limited number of countries were found to be complex and varied by country; the shorter duration of protection and probable reduced impact of acellular vaccines on pertussis infection and transmission likely played a role.

Following a thorough review of evidence leading to new recommendations by the Strategic Advisory Group of Experts on immunization, WHO published an updated position paper with revised guidance on the choice of pertussis vaccine[4]. The guidance includes recent evidence on the use of additional strategies, particularly on vaccination during pregnancy, to prevent early infant mortality.

Two types of pertussis vaccines are available: whole cell (wP) and acellular (aP). Protection can be achieved through primary vaccination with either vaccine, and both vaccines have excellent safety records. A switch from wP to aP vaccines for the primary schedule should, however, only be considered if additional periodic boosters or maternal immunization can be assured and sustained. National programmes currently administering wP vaccination should continue to use wP vaccines for primary vaccination.

Although vaccination can prevent pertussis in adolescents and adults, there is insufficient evidence that vaccine boosters in these groups can reduce the burden of severe pertussis in

[3] http://www.who.int/immunization/diseases/poliomyelitis/endgame_objective2/en/
[4] http://www.who.int/wer/2015/wer9035/en/

infants. However, vaccination of pregnant women appears to be the most cost-effective additional strategy for preventing disease in infants too young to be vaccinated.

2. Strengthening immunization service delivery

2.1. The WHO Vision and Mission in Vaccines and Immunization, 2015-2030.

While the Global Vaccine Action Plan (GVAP) covering 2011-2020 was created to end the inequity in vaccination worldwide, and hence to save millions of lives, a mid-term review conducted by SAGE[5] identified several factors that appear to be causing patchy and slow implementation, including an increasingly crowded operating environment and a lack of defined responsibilities and accountability among partner agencies.

WHO's Vision and Mission in Vaccines and Immunization 2015-2030[6] describes WHO's mandate and strategic directions in achieving the goals of the of GVAP, across all areas of work and all levels of the organization, through the current decade and the next. Recognizing the importance of immunization among the most powerful and cost-effective interventions in public health, and the expanding scope and increasing complexity of immunization programmes, the WHO *Vision and Mission* was developed to create a unifying vision across all WHO departments and levels on immunization and thus to enable WHO to anticipate and respond more effectively to opportunities and challenges in future.

To develop the *Vision and Mission*, a number of work streams were conducted throughout 2015, including regional consultations, implementation of an expectations survey targeting partner agencies and donors, review of previous and current strategies and their impact, analysis of existing strategies and background documents, and a historical review of past trends and success factors in immunization. Internal consultations also took place with WHO staff at all levels, with a specific focus on identifying areas where the agency has a unique role and comparative advantage, and non-priority areas that could be phased out.

The *Vision and Mission* reasserts WHO's global leadership role in immunization through redefined normative responsibilities, policy development, expert advice and inter-agency priority-setting. It also brings forward WHO's renewed focus on technical guidance, knowledge management and data for decision-making. The document will be referenced to guide internal decisions about where and how to maximize resources and which strategic directions should be deployed over this exciting period of transition and expansion in the field of vaccines and immunization.

[5] http://www.who.int/immunization/global_vaccine_action_plan/SAGE_DoV_GVAP_Assessment_report_2014_English.pdf
[6] weblink

2.2. Global Routine Immunization Strategies and Practices to achieve universal and sustainable coverage.

In 2015, the Global Routine Immunization Strategies and Practices (GRISP) document was developed by WHO and finalized with the support of global partner agencies. Key routine immunization staff from WHO and partner agencies participated in a steering committee which also defined the key directions that would take routine immunization forward during the next five years. Furthermore, the GRISP provides a comprehensive overview of routine immunization strategies and a structured approach to improving routine immunization. Finally, it distinguishes between strategies and activities that are designed to raise vaccination coverage from strategies and activities designed to strengthen the immunization delivery system. While these components are closely linked and influence each other, it is operationally useful to separate them.

The GRISP framework outlines the specific strategies and activities required to ensure that routine immunization services are accessible to all—regardless of who they are or where they live. To equip routine immunization programmes for success in every country, GRISP recommends that national governments, partner agencies and donors focus on and invest in the following nine areas:

- **National team**: The most important factor for all other eight investments to succeed: A qualified national team—supplied with sufficient resources and authority—to manage effectively their national immunization program.
- **Strategies to reach**: Tailored strategies that identify under-vaccinated and unvaccinated individuals and provide them regularly with the vaccines they need.
- **Strategic and multiyear plans**: Strategic multiyear plans and operational annual plans outlining and coordinating strategies and activities, with progress monitored on a quarterly basis.
- **Operational level funding**: Assurance that sufficient funds are available for expenditure at operational level when required.
- **Vaccinator capacity**: Regular and systematic capacity building, skills development and supportive supervision for vaccinators and their district managers.
- **Modern vaccine supply chain**: Modernized vaccine supply chains and management to ensure the correct amounts of the right potent vaccines are available at each vaccination session.
- **Accurate information system**: An information system that identifies and tracks each individual's vaccination status.
- **Life course vaccination**: Expanded routine immunization schedules that cover individuals' entire life course.
- **Community support**: Shared responsibility for immunization delivery between communities and the immunization programme to reach uniformly high coverage through high demand and convenient, user-friendly services.

2.3. Strengthened "hub" collaboration between WHO and UNICEF to optimize immunization supply chains.

Effective Vaccine Management (EVM) assessments are designed to evaluate the performance of national immunization supply chains from end-to-end and benchmark performance against international best-practice standards. In 2015, over 80 member states received support from WHO and UNICEF to conduct EVM assessments as part of an initiative which was originally launched in 2010. The result of these assessments revealed that most countries face chronic vaccine shortages due to weak stock management and forecasting practices; are damaging expensive vaccines by storing them in non-compliant or poorly maintained cold chain systems; are unable to introduce new vaccines due to cold chain storage constraints; and vaccines are wasted from poor handling and vaccine management practices by health workers. Current performance of in-country supply chain and logistics systems cannot ensure the uninterrupted availability of vaccines up to service delivery points. Furthermore, vaccines that have been exposed to deficient cold chain systems may lack potency due to heat or freeze damage prior to vaccination and, thus, compromise effective coverage.

In response to these mounting concerns and convinced by the need to build on the successes the EVM initiative, WHO and UNICEF have intensified their collaboration in 2015 and created a joint multi-year workplan resourced by the Bill & Melinda Gates Foundation and the GAVI Alliance. The centrepiece of this collaboration is the implementation of a four-step strategy for continuous immunization supply chain improvements, optimization and innovation in countries.

This new comprehensive approach to EVM (or cEVM) and renewed technical assistance framework will ultimately lead to immunization supply chains that are designed to maximize efficiency, effectiveness, agility and responsiveness to the needs of today's and tomorrow's immunization programmes. They will be sufficiently robust to continually adapt to and comply with WHO and UNICEF recommended vaccine management standards and policies. Future supply chains will adopt proven cost-effective technological and systems solutions that support coverage and equity improvement objectives. They will be operated by skilled health care workers managing the supply chain with key performance indicators, and adequately funded using health system strengthening resources.

2.4. Immunization sustainability.

In 2015, important investments designed to enhance the sustainability of national immunization programmes came to fruition. Sustainability in this context refers to the durability of immunization systems and processes in countries that are not eligible for external financial or other support or whose current support is due to be reduced or eliminated in the near future.

WHO led the development of a strategy to enhance immunization sustainability with particular focus on middle-income countries (MICs). Since MICs currently generate about two-thirds of all global vaccine-preventable mortality, and many are either ineligible for

external financial support from agencies such as the GAVI Alliance or will soon lose eligibility, immunization sustainability represents an issue of growing urgency.

The principal immunization partner agencies, including the Agence de Médècine Preventive, the Bill & Melinda Gates Foundation, the GAVI Alliance, the Sabin Vaccine Institute, UNICEF and the World Bank, contributed to the development of the strategy, as well as national governments, civil society organizations, and vaccine manufacturers. The strategy guides WHO's approach to sustainability in four priority areas: i) strengthened decision-making on immunization, ii) enhanced national political commitment and immunization financing, iii) increased demand for vaccination services and iv) enhanced access to affordable and timely vaccine supplies.

While some additional and reliable funding will be required by many countries in order to operationalize this vision, WHO is already providing technical support on cost-benefit and cost-effectiveness analysis to rationalize vaccine choices and the strengthening of institutions for evidence-based decision-making in immunization. Furthermore, countries are receiving technical assistance to develop their multi-year immunization plans, including the quantification of resource requirements. WHO routinely analyses and disseminates vaccine price information to inform country and global policy-making and is working to strengthen regional vaccine procurement mechanisms. WHO also provides technical support to countries whose immunization programmes enter the process of transition from GAVI Alliance support to self-sufficiency.

2.5. Ensuring that vaccines and immunization devices are of assured quality.

Vaccine prequalification is a WHO-led activity with the primary purpose of ensuring that vaccines purchased by UN agencies are consistently safe and effective for use by national immunization programs. Driven by the stringent quality requirements of donors and procurers, WHO prequalification offers manufacturers a well-established mechanism for accessing markets for products that meet internationally agreed quality norms and standards. Furthermore, the previously independent prequalification streams for diagnostics, medicines, vaccines and immunization devices have been merged to provide assurance on the quality, safety and efficacy of these products for international procurement.

WHO has introduced efficiencies designed to shorten the vaccine prequalification process, achieving the reduction of the timeframe for prequalification in 2015 from 360 to 270 days. For example, WHO prequalified a second affordable oral cholera vaccine (OCV), which is expected to double current global OCV supply, within the reduced timeframe. Through its highly participatory and collaborative activities, the WHO Prequalification Team (PQT) leveraged these well-established processes to increase the capacity of manufacturers and regulators to implement stringent quality standards. To facilitate this effort, WHO published procedures for the collaborative national registration of prequalified pharmaceutical medicines and vaccines. The new procedures were implemented on a pilot basis for the registration of inactivated poliovirus vaccines whose deployment represents an essential step in the polio end game strategy.

The PQT also provided guidance on regulatory and WHO prequalification requirements for specification of an on-label extended controlled temperature conditions for priority vaccines. Furthermore, the PQT published guidelines for vaccines (and separately for diagnostics and pharmaceutical medicines) to be used in response to Public Health Emergencies of International Concern.

The WHO Immunization Practices Advisory Committee developed guidelines to extend the vaccine prequalification process to ensure that existing and future products comply with operational requirements for programmatic suitability, primarily, that products come appropriately packaged and presented for field use. During 2014-15, WHO reviewed 16 previously prequalified vaccines that failed to comply with the new programmatic suitability guidelines, withdrawing prequalification from several products or requesting manufacturers to modify product presentation or provide additional data, for example, on thermostability characteristics.

2.6. Licensing vaccines for use in a Controlled Temperature Chain, facilitating the logistics of immunization campaigns.

The need to maintain modern vaccines in refrigerated transport and storage has complicated vaccine supply and delivery, especially in countries with tropical climates and unreliable energy supply. Consequently, WHO has been actively exploring the feasibility of distributing certain heat-stable vaccines in a Controlled Temperature Chain (CTC) to remote and difficult-to-access regions. For a vaccine to be labelled for and used in a CTC, it must be able to tolerate ambient temperatures of at least +40°C for a minimum of three days immediately prior to administration. The meningococcal type A vaccine, MenAfriVac, was the first such vaccine to be successfully licensed, WHO prequalified, and implemented with CTC. Since that initial success in 2012, four more vaccines have been licensed for CTC: two oral cholera vaccines in 2014 and 2015, a pneumococcal conjugate vaccine in 2015, and as of February 2016, a human papillomavirus (HPV) vaccine. Additional efforts are under way in support of CTC compatibility for further vaccine products, including hepatitis B and rotavirus vaccines.

Progress was achieved through dialogue with vaccine manufacturers, as well as with key partner agencies such as PATH and Médecins Sans Frontières. In collaboration with the Essential Medicines and Health Products Department, manufacturers also received guidance on regulatory and WHO prequalification requirements. An assessment of manufacturers' views on CTC was conducted to identify barriers to the process of getting licensure for more CTC-compatible vaccines.

In 2015, WHO launched a series of advocacy tools for use at regional and country level including an infographic and a film, to explain the benefits of CTC and to create demand for vaccines licensed for CTC. WHO has successfully implemented an effective CTC strategy during several meningococcal type A vaccination campaigns, and is committed to

developing detailed implementation guidelines for upcoming new products to be delivered in a CTC.

Significant operational benefits of using CTC have been observed, including freedom from the need to carry and replace ice packs continually during vaccination sessions, facilitating travel to more remote populations, allowing more vaccine vials to be transported in the vaccine carriers, and removing the risk of freezing vaccine due to contact with frozen ice packs.

2.7. Developing capacity for vaccine safety monitoring in African countries.

As the number and variety of available vaccine products keeps increasing, and as many vaccine-preventable diseases are coming under effective control, there is also greater global attention on adverse reactions following vaccination. In 2012, WHO published the Global Vaccine Safety Blueprint, a strategy designed to ensure that all everyone everywhere is protected by safe and effective biologicals. The Blueprint's first strategic goal is to ensure that all countries establish a minimum capacity for vaccine safety monitoring. This includes creating an effective mechanism to report vaccine safety concerns and unusual events, ensuring access to adequate resources for investigating serious events, committing to share information with other countries, and developing a communication strategy.

The Global Vaccine Action Plan (GVAP) established a vaccine safety indicator to monitor countries' ability to detect and report adverse events following vaccination. In recent years, several countries in Asia, Latin America and the Middle East have made considerable progress in establishing vaccine safety systems and have shared their experience through the Global Vaccine Safety Initiative (GVSI). However, analysis of data communicated to WHO in 2014 showed that less than 20% of countries in the WHO African Region were in compliance with the GVAP indicator, the smallest proportion among the six WHO Regions.

To address the challenge in the WHO African Region, four multi-country workshops were held with representatives from 29 countries during 2014 and 2015. Based on the established indicators for vaccine safety systems, countries identified gaps, prepared work plans and prioritized activities. With support from the GAVI Alliance, technical assistance was provided by the WHO African Regional Office and HQ, deploying experts from a GVSI roster.

The main challenge to expanding this initiative further is the low rate of adverse event reporting in many countries. Success in establishing monitoring systems more widely will require that all national and international stakeholders in immunization embrace the imperative to systematically report, investigate and respond to vaccine safety concerns and unusual events.

3. Vaccine assessment and monitoring

3.1. Broad dissemination and utilization of Joint Report Form databases for decision-making by WHO and partner agencies.

In an annual submission called the Joint Report Form, WHO and UNICEF collect standardized, official national data from all Member States including the reported cases of selected vaccine-preventable diseases, vaccination coverage, vaccine supply, recommended immunization schedules and other information on the structure, policies and performance of national immunization systems. The data are consolidated and disseminated through both WHO and UNICEF web sites. These data are also made available as an application (app) for use with computer tablets in the six official UN languages. The free app generates country profiles, summary tables, graphs and maps using data that are updated annually.

The data are of particular value in tracking the implementation status of the Global Vaccine Action Plan (GVAP) and the Regional Vaccine Action Plans (RVAPs). GVAP was endorsed by all WHO Member States in 2012 at the World Health Assembly (WHA), and both the GVAP and RVAPs are key frameworks to guide immunization strategies and measure performance towards quantifiable targets at global and regional levels. Monitoring reports on GVAP progress, developed using data reported by countries, are presented to the WHA each year.

Data made available on the WHO and UNICEF websites and through the free app have been accepted globally as the most comprehensive source data to which reference is made throughout the public health community. For example, data are utilized for:

- monitoring global health status and assessing health trends, one of the WHO and UNICEF core functions;
- monitoring progress towards the UN Sustainable Development Goals;
- one of the main data sources for calculating the WHO and UNICEF estimate of national vaccination coverage;
- guiding global and regional immunization policies and strategies;
- informing vaccine-preventable disease burden estimates and trends; and
- maintaining global databases and publications, such as WHO country summaries[7] and UNICEF's annual publication State of the World's Children.

3.2. Updated guidance on vaccination coverage and serological surveys.

Reliable and timely data are essential for accountability and evidence-based decision-making at all levels of the health system. Member States, WHO and immunization partner agencies therefore all continue to call for better quality data. During 2015, WHO worked across all levels of the Organization and with partner agencies to develop and disseminate several important tools designed to improve the quality and utilization of immunization data use and quality. Several practical guidance documents were produced: **A practical Guide**

[7] Available at http://www.who.int/immunization/monitoring_surveillance/en/

for the design use and promotion of Home-Based Records in Immunization Programmes (available in English and French); an **e-learning module** on coverage monitoring (available on iLearn and on the WHO extranet); guidance on **Assessing and Improving the Accuracy of Target Population Estimates for Immunization Coverage; a data quality assessment module** to be integrated into the overall methodology for National Immunization Programme reviews, and a working draft of a revised **WHO Vaccination Coverage Cluster Survey Reference Manual** that provides guidance on the design of vaccination coverage surveys, from protocol design, to sample size calculation, cluster selection, field data collection and interpretation of survey results. This latter draft is undergoing pilot testing in the field prior to its finalization in 2017.

Similarly, draft guidance on another document entitled **Collecting, Assessing, and Using Immunization Data** is being circulated for feedback. This document builds on existing work (1) to provide a critical and systematic way to assess monitoring systems and national immunization data, (2) to explore ways how data can be better analysed, visualized, and used, and (3) to describe ways in which information and communication technology can be harnessed for these purposes. In December 2015, a global workshop was convened to disseminate and discuss the proposed new vaccination survey methodology, as well as methods for data and systems assessments covering the entire process from situation diagnosis to action plan. The work on the area of immunization data use and quality will contribute to WHO's continued leadership in the area of immunization monitoring and evaluation, to a more purposeful approach to data quality, and eventually to more effective national systems, able to measure and demonstrate better health outcomes.

3.3. Identifying new vaccine-preventable causes of child diarrhoea using novel laboratory technology.

Diarrhoea is one of the leading global causes of mortality and morbidity in children under 5 years of age, caused by many different pathogens. Vaccines are available to prevent diarrhoea caused by rotavirus, while vaccines are under development against pathogens such as *Escherichia coli*, Norovirus and Shigella.

Since 2008, WHO has coordinated the Global Rotavirus Sentinel Site Surveillance Network to monitor the burden and epidemiology of rotavirus disease and to serve as a platform to evaluate the impact of rotavirus vaccine. In 2014, 45,320 cases of diarrhoea in children under 5 years of age were reported from 105 surveillance sites in 51 countries. Nearly a third (31%) of these cases tested positive for Rotavirus. However, the samples were not tested for other pathogens for which vaccines are currently not available.

In order to add to the current limited data on the global epidemiology of diarrhoeal pathogens and to guide the development and use of future vaccines, a novel diagnostic test, the TaqMan Array Card (TAC), was tested through the rotavirus surveillance network. Specimens were gathered and tested using the TAC for more than 25 enteric pathogens other than Rotavirus. With support from the Bill and Melinda Gates Foundation, the University of Virginia, and the U.S. Centers for Disease Control and Prevention, TAC

laboratory testing capacity was established at five regional references laboratories. More than 1,200 specimens were tested from 11 countries in Africa, Asia, and the Americas. The first phase of the project was completed in 2015 and showed that this novel diagnostic testing platform could be used successfully in diagnostic laboratories globally to identify the causes of diarrhoea in children. Rotavirus, Escherichia coli, Norovirus and Shigella were found to be the most common diarrhoeal pathogens in children, indicating that vaccines should prove effective in lowering the global burden of diarrhoeal mortality and morbidity.

4. Accelerating vaccine-preventable disease control.

4.1. Coordinating the introduction of injectable polio vaccine in 81 countries and preparing for the globally synchronized withdrawal of type 2 oral polio vaccine in 155 countries.

In preparation for the phased withdrawal of trivalent oral polio vaccine (OPV) starting in April 2016, all countries were required to include one dose of inactivated polio vaccine (IPV) in the national immunization schedule before the end of 2015.

At the start of 2015, only eight of the 126 countries exclusively using OPV had already introduced IPV into their routine immunization programmes. Introducing IPV in the 118 remaining countries represented an unprecedented and challenging task, from understanding the rationale, to generating public and professional commitment to introduce IPV within the agreed timeframe. This required intense advocacy, coordination, and frequent dialogue and information-sharing with regions and countries.

The number of IPV introductions surged during the second half of 2015, so that a total of 75 countries completed the task during 2015. Due to global supply constraints, almost 30 low-risk countries have seen their introductions postponed to 2016. The impact of the delays is continually assessed by the Immunization Management Group (IMG) through a supply task force (WHO, UNICEF, GAVI Alliance, and the Bill & Melinda Gates Foundation), using prioritization criteria endorsed by SAGE. In October 2015, SAGE reaffirmed that the globally synchronized switch from trivalent to bivalent OPV, eliminating the type 2 vaccine virus, should occur in April 2016, in all 155 countries and territories, despite delayed introduction and supply constraints affecting some countries.

By the end of 2015, all countries had initiated the development of their national switch plans, and the few remaining countries were being closely supported by WHO Regional Offices.

WHO partner agencies including the Clinton Health Access Initiative, UNICEF, the US Centers for Disease Control and Prevention, and the Task Force for Global Health and have been continually engaged in orientation and planning activities with regions and countries.

This intensive collaboration between global and regional agencies has ensured that countries would comply with the timelines of the Polio Eradication and Endgame Strategic Plan.

4.2. Strengthened case-based surveillance and new tools to improve vaccination campaign quality to accelerate progress towards measles and rubella elimination.

Using a model developed earlier, WHO updated and published global and regional measles mortality estimates in 2015[8]. These data reconfirmed that measles vaccination is one of the best buys in public health and has saved an estimated 17.1 million lives since 2000.

In accordance with SAGE recommendations and putting into practice current technical guidance, WHO assisted six countries to introduce a routine second dose of measles vaccine into their childhood immunization schedules in 2015. New guidelines on introducing rubella vaccine into national immunization programmes were published in 2015[9]. WHO provided technical assistance to eight countries to introduce rubella vaccine into their national immunization schedules in 2015.

In 2015, the Measles and Rubella Initiative provided over $15 million in funding to 8 countries for urgent measles outbreak response vaccination. The countries supported were Djibouti, Democratic Republic of the Congo, Ethiopia (targeting 21 high-risk and drought-affected districts), Liberia (where measles outbreaks followed disruption to immunization services caused by the Ebola virus outbreak), Kyrgyzstan, Nepal (targeting 14 districts heavily affected by earthquakes), Somalia, and Sudan.

Performance during supplementary immunization activities (SIAs) with measles-containing vaccines has declined in recent years. In response, in 2015 WHO developed several new tools for improving performance, including a programme risk assessment tool[10], a readiness assessment tool, and new tools for monitoring coverage. WHO provided technical assistance to more than 25 countries conducting measles or measles-rubella SIAs in 2015. In addition, special advocacy visits were made to the Democratic Republic of Congo, Ethiopia and Nigeria to stress the need for strong country commitment to achieving high equitable vaccination coverage during SIAs.

In 2015, 98% of countries globally had access to standardized quality-controlled testing through the WHO Global Measles and Rubella Laboratory Network which processed over 250,000 clinical specimens for measles diagnosis. Of the 11 measles virus genotypes detected globally during 2005-2010, five have not been detected since 2011, suggesting that they may have been eliminated. Furthermore, despite the increasing quality of measles genotype surveillance, the number of virus variants has decreased, indicating progress in the interruption of endemic virus transmission.

[8] http://www.who.int/wer/2015/wer9046/en/
[9] http://apps.who.int/iris/bitstream/10665/184174/1/9789241549370_eng.pdf?ua=1
[10] http://www.ncbi.nlm.nih.gov/pubmed/25976980

4.3. Significant progress towards maternal and neonatal tetanus elimination.

Fifty years after a cheap and efficacious vaccine became available, by the late 1980s an estimated 787,000 neonatal deaths annually were still caused by tetanus. Global efforts following a 1989 World Health Assembly resolution calling for the elimination of neonatal tetanus (NT) led to a reduction in mortality to an estimated 200,000 deaths by 2000 and a further reduction to 49,000 deaths by 2013. In a remarkable achievement, of the 59 countries classified as high priority for Maternal and Neonatal Tetanus Elimination (MNTE) as of 2000, 38 of these countries, including China and India, achieved elimination by the end of 2015. Globally, 130 million women of reproductive age (WRA) have been reached with at least two doses of tetanus toxoid (TT) vaccine through vaccination campaigns between 1999 and 2015.

The WHO-recommended strategies implemented by countries leading to the attainment of MNTE by 2015, and confirmed through validation assessments, include the high-risk approach that is initiated by the implementation of three properly-spaced rounds of TT campaigns in high-risk districts; strengthening routine delivery of TT vaccine and extending service delivery to the school setting; supporting initiatives to improve the proportion of births occurring in health facilities and/or assisted by skilled birth attendants; encouraging clean umbilical cord care practices; and active surveillance for NT. In addition, government commitment through comprehensive micro-planning, early and active community engagement and the timely availability of resources from partner agencies has greatly contributed to the success of the programme.

In 2015, MNTE pre-validation assessments were conducted in three countries (Democratic Republic of Congo, Indonesia and Niger). Three more countries (Cambodia, India and Mauritania) were validated for the attainment of MNTE. Partial MNTE validation was confirmed in 16 of the 17 Provinces of the Philippines and TT vaccination campaigns were implemented in nine countries targeting around 9.5 million WRA.

4.4. Launch of the post-Meningitis Vaccine Project transition of key interventions into national immunization programmes.

The Meningitis Vaccine Project (MVP), a partnership between WHO and PATH which ran from 2001 to 2014, was developed with the goal of eliminating epidemic meningitis as a public health problem in sub-Saharan Africa. The MVP partnership achieved its objective of developing, testing, licensing, and introducing a safe, efficacious and affordable meningococcal conjugate vaccine to the field with over 215 million individuals vaccinated in just five years. However, to protect everyone living in the African meningitis belt against invasive meningococcal disease in a sustainable manner, the effective transition of key interventions into national routine immunization and surveillance programmes is imperative.

In 2015, the post-MVP transition of key interventions into national immunization programmes was implemented. Two components of the critical first year of the transition

deserve special mention. Firstly, the continuation of the MenAfriVac® vaccine roll-out across countries of the sub-Saharan African meningitis belt was extended to an additional 20 million persons aged 1-29 years in two more countries (Ethiopia [final phase] and Guinea). Secondly, the first eight meningitis-belt countries applied to the GAVI Alliance for funding to introduce the vaccine into the routine immunization programme following licensure and WHO prequalification (Burkina Faso, Central African Republic, Chad, Ghana, Mali, Niger, Nigeria and Sudan)[11].

The success of transition activities in 2015 has set the scene for the future. Among the 10 countries that have yet to conduct full campaigns, six are ready to conduct their campaigns in 2016: either nationwide (Central African Republic, Guinea Bissau and South Sudan), or selectively in high-risk areas (Democratic Republic of Congo and Uganda). The remaining five countries are expected to conduct campaigns in high-risk areas in 2017 (Burundi, Eritrea, Kenya, Rwanda and Tanzania). The remaining 18 meningitis belt countries are expected to apply for funding to introduce the vaccine into the routine immunization programme in the next couple of years.

4.5. Updated guidance and new tools to accelerate the implementation of maternal influenza vaccination.

The strategy of maternal immunization has the potential to reduce vaccine-preventable diseases in pregnant women as well as in their newborn infants. In 2012, WHO modified its influenza vaccine policy position by recommending that pregnant women be prioritized for influenza vaccination in countries expanding or initiating influenza vaccine programmes. Despite this policy recommendation, many low- and middle-income countries have still not adopted maternal influenza immunization policies, with many countries citing data gaps in disease burden, vaccine impact, and cost-effectiveness.

In 2015, WHO strengthened the evidence base for decision makers by conducting extensive reviews of influenza morbidity in pregnant women and newborn infants., as well as reviews of influenza vaccine performance in these groups. WHO convened a working group of international experts in influenza epidemiology, statistics, and modelling for the purpose. WHO is also providing technical support for the development and pilot testing of several health economics tools designed to assist countries to determine the costs of influenza illness and vaccine programs, as well as the cost-effectiveness of influenza vaccines.

In addition, WHO has launched a number of activities designed to accelerate introduction of maternal influenza immunization. A global group of experts is assisting WHO to develop implementation guidance for maternal influenza immunization in low- and middle-income country settings. WHO is also working with industry and regulatory agencies to ensure sufficient influenza vaccine supplies globally and to provide guidance on interpretation of product label statements regarding risk to pregnant women. Through these activities, the evidence base for recommending maternal influenza immunization will be greatly

[11] http://www.afro.who.int/en/media-centre/pressreleases/item/8360-meningitis-a-nearly-eliminated-in-africa-through-vaccination.html

expanded. Countries will have much more data to make informed decisions regarding the costs and benefits of introducing maternal influenza immunization into routine public health programs. WHO implementation guidance on maternal influenza immunization will accelerate national programme development and provide a platform for future vaccine introduction into routine antenatal service delivery.

5. Immunization research and innovation.

5.1. Coordination and implementation of Ebola vaccine research and product development.

During 2014 and 2015, a large-scale outbreak of Ebola disease which was declared a Public Health Emergency of International Concern affected a number of West African countries. The slow progress in controlling the outbreak underscored the urgent need for a vaccine against Ebola virus. An unprecedented and largely collaborative effort built on the availability of a number of candidate vaccines that could enter into clinical phase evaluation. In the midst of the outbreak, and facing several challenges and criticisms, a series of international consultations and activities were led by WHO as a contribution to the unprecedented global efforts to develop and evaluate an Ebola vaccine.

WHO's contribution included coordination of consortia that enabled accelerated testing of the two lead Ebola vaccine candidates in North America, Europe and Africa. WHO assumed a leading role in the design, conduct and analysis of an important Phase III trial in Guinea, the only vaccine trial that successfully estimated the efficacy of an Ebola vaccine. Another critical role was to enable comparative immunogenicity testing from different clinical trials and different vaccines.

WHO consulted urgently and widely, fostered interactions with international scientific institutions, ethical, and regulatory bodies, vaccine development and public health partner agencies, industry and funders' groups, and participated in consortia to facilitate Ebola vaccine assessments. WHO also fostered key activities to ensure the optimal policy and deployment plans for Ebola vaccines, if and when licensed. The end result of this work was to highlight several safe and immunogenic vaccine candidates, laying the groundwork for regulatory submissions for consideration of licensure. This work will enable access to safe and effective Ebola vaccines when the next outbreak occurs.

Furthermore, the work in Ebola proved critical in the follow-on development of WHO's Research and Development (R&D) Blueprint which provides a platform for accelerated research and product development for outbreaks of international concern. This R&D Blueprint initiative has already proven valuable in preparing the response to the ongoing public health emergency due to Zika virus.

5.2. Development of a partners' framework and a collaborative plan for the deployment of first generation Ebola vaccines.

The largest and most complex Ebola virus outbreak since the virus was first discovered in the Democratic Republic of Congo in 1976 occurred in west Africa during 2014-15. More cases and deaths were reported in this outbreak than in all previous outbreaks combined. In 2014, WHO declared the outbreak a Public Health Emergency of International Concern that required the implementation of extraordinary measures and collaboration to interrupt transmission and control the epidemic, including comprehensive vaccine research and development.

The inter-agency Global Ebola Vaccine Implementation Team (GEVIT) was convened and led by WHO to develop a coordinated plan to support affected countries in their efforts to prepare for the potential use of Ebola vaccines. GEVIT brought together the most affected countries (Guinea, Liberia and Sierra Leone) with partner agencies involved in vaccine policy development and procurement (Bill & Melinda Gates Foundation, GAVI Alliance, UNICEF, USAID, US Centers for Disease Control and Prevention, and WHO). In 2015, through a structure consisting of a Steering Group and three Working Groups (Vaccine supply, allocation and procurement; Country implementation; and Monitoring, surveillance and impact evaluation), GEVIT developed a "Country Guide for Use of Ebola Vaccine in Outbreak Response" which includes comprehensive technical details of Ebola candidate vaccines in clinical development. This represents a valuable resource for governments and partner agencies as they plan for the potential use of Ebola vaccines during future outbreaks. A mechanism for the management and deployment of Ebola vaccine has also been proposed through the establishment of an International Coordinating Group on Ebola Vaccine (ICG-EBOV)[12].

In 2015, countries and partner agencies agreed that GEVIT should continue functioning through 2016 and beyond, in order to ensure the integration of vaccine development efforts with Ebola preparedness and response activities as well as routine immunization service delivery at all levels. GEVIT will continue to facilitate work with partner agencies to secure adequate Ebola vaccine supply and to consolidate the establishment of the ICG-EBOV.

5.3. Publication of a WHO position paper on public disclosure of all interventional clinical trial results.

Several studies and audits in recent years showed that the results of many clinical trials remain unreported or reporting is delayed for years. This leads to major bias in information available for decisions regarding public health interventions or the allocation of resources.

To address this problem, in 2015 WHO published a new position paper on the public disclosure of clinical trial results[13] . The position paper was developed taking into account

[12] http://www.who.int/healthsystems/publications/vaccines-deployment-workshop/en/
[13] www.who.int/ictrp/results/reporting

more than 700 responses to a public consultation process. The WHO statement defines reporting timeframes, calls for reporting of the results of previous unpublished trials, and outlines steps to improve linkages between clinical trial registry entries and their published results. WHO's position is that the protocol pre-specified key findings from clinical trials should be made publicly available within 12 months of study completion by posting to the results section of the primary clinical trial registry. The International Committee of Medical Journal Editors confirmed that posting results in clinical trial registries will not impact subsequent journal publication. In addition, the WHO statement recommends timelines for reporting of findings in the peer reviewed literature, noting that several journals are equally willing to publish negative or inconclusive results as to publish positive results (for example, the journals *PLoS* and *Trials*).

Since WHO and the International Committee of Medical Journal Editors recommended that all clinical trials be prospectively entered into clinical trial registry databases that are compliant with WHO's norms, registration of clinical trials has become the norm, although compliance remains incomplete. However, several recent audits have confirmed that reporting bias remains high across several classes of medical products. Consequently, WHO reconfirmed its support for universal compliance with prospective clinical trial registration and added its voice to calls for timely public disclosure of results from all interventional clinical trials, and continues to provide technical support to the global network of interventional clinical trial registries.

5.4. Information sharing to accelerate the response to public health emergencies.

The WHO Research and Development (R&D) Blueprint was established in 2015 and constitutes a global strategy and preparedness plan to ensure that targeted R&D is ready to strengthen the response to public health emergencies by generating critical research information and bringing medical technologies to patients during epidemics. The Blueprint aims to reduce the time between the declaration of an international public health emergency and the availability of effective tests, treatments and vaccines that can be used to save lives and resolve crises.

WHO convened a R&D Blueprint consultation in 2015 in recognition of the wider need to streamline global mechanisms of timely and transparent data dissemination in the context of public health emergencies. The consultation addressed the urgent need for accelerated data sharing, and a consensus statement was published which described the core principles to improve information sharing in future emergencies.

The current public health emergency caused by the Zika virus has demonstrated that implementation of these principles remains of paramount importance. WHO launched the Zika Open initiative in an attempt to make all manuscripts related to research on Zika virus publically available within 24 hours of receipt, while peer review continues in parallel. A joint statement from over 30 leading global health bodies including academic journals, non-governmental organizations, research funding agencies and institutes was released early in 2016. Signatories committed to sharing data and results relevant to the Zika crisis and

future public health emergencies as rapidly and transparently as possible. The joint statement represents a consensus set of principles for data and results sharing, and confirms that pre-publication information sharing has been accepted by leading medical journals and funders as the established global norm in the context of public health emergencies.

5.5. Establishing a maternal immunization clinical development pathway for Respiratory Syncytial Virus vaccine candidates for infants.

There is an urgent unmet public health need for interventions to prevent Respiratory Syncytial Virus (RSV) infection, particularly in neonates and infants in low- and middle-income countries. Maternal immunization could be one of the most effective ways to reduce the risk of neonatal infection and death by passive transfer of maternal RSV antibodies. Although influenza and pertussis vaccines and tetanus toxoid are currently recommended by WHO for immunization of pregnant women, the initial licensure of an RSV vaccine targeting this specific population group will create regulatory precedent. Understanding the most expeditious pathway to regulatory approval of this new class of vaccines for RSV is particularly urgent as some candidates are in advanced clinical stage development, with one entering phase III in 2015.

In 2015, WHO convened a first consultation on RSV vaccine development with vaccine developers, academics, regulators and donors, and achieved consensus on case definitions for RSV disease, considerations for clinical efficacy endpoints as well as the clinical development pathway for active and passive immunization trials in maternal and pediatric populations. The goal is to develop recommendations on high quality, safe and efficacious RSV preventive interventions for global use through (1) maternal/passive immunization to prevent RSV disease in infants less than 6 months, and (2) pediatric immunization to prevent RSV disease in infants and young children once protection afforded by maternal immunization wanes.

The recommendations from this consultation have been published[14] and have guided subsequent discussions with vaccine developers, regulators and other key stakeholders. This consultation also formed the basis for developing draft Preferred Product Characteristics and a draft technology roadmap to help guide development of RSV vaccine candidates to be presented at the second WHO consultation in 2016.

5.6. Convening the global community to plan the next steps towards licensure of microarray patches for vaccine delivery.

In line with the Global Vaccine Action Plan (GVAP), WHO's mission is to increase equitable vaccination coverage against vaccine-preventable diseases, as well as to accelerate the development, approval and implementation of new vaccines and delivery technologies. Microarray patches (MAPs) are a novel vaccine delivery methodology that have the

[14] http://ac.els-cdn.com/S0264410X15007677/1-s2.0-S0264410X15007677-main.pdf?_tid=2a9bc980-d5a1-11e5-b704-00000aab0f6c&acdnat=1455732575_d6642c1a095efbbca927d2b090da2ce8

potential to significantly improve vaccination coverage by making vaccination faster, safer and more acceptable by replacing needles and syringes, as well as removing the need for vaccine transport and storage in a cold chain, enabling vaccine administration by minimally-trained volunteers and virtually eliminating vaccine wastage.

MAPs are currently in preclinical development for a number of existing vaccines, including influenza, tetanus toxoid, measles-rubella (MR), inactivated poliovirus vaccine, as well as for vaccines currently in development such as inactivated rotavirus, and dengue vaccines. However, several technical aspects still need to be resolved with respect to the appropriate product development strategy and the pathway to licensure, since MAPs are considered a novel combination vaccine product.

In 2015, following up on an earlier meeting on a range of novel vaccine delivery technologies, WHO convened a workshop with MAP developers, vaccine manufacturers, regulators, funders and other key stakeholders. The workshop objectives were to better define and address the technical, financial and programmatic challenges facing product development, to identify scientifically-based evidence where available, and to propose research priorities where gaps still exist. Early clinical data with MAPs and influenza vaccine are now emerging and are encouraging with respect to end user acceptability, safety and immunogenicity. The field eagerly awaits clinical data for other vaccines such as polio and MR, whilst continuing to develop an improved regulatory route to licensure, and studies of the potential cost-effectiveness of these novel delivery devices.

The workshop raised awareness of the MAP platform's potential to transform the delivery of vaccines to hard-to-reach populations and thus increase vaccination coverage. However, the challenges associated with product development were identified in order to inform strategies for future investment. The Bill & Melinda Gates Foundation, PATH and WHO are planning additional activities in 2016 to incentivize the engagement of vaccine manufacturers and MAP developers.

5.7. Publication of a journal supplement describing the experience and results of the Meningitis Vaccine Project.

The Meningitis Vaccine Project, a partnership between WHO and PATH, had a single goal: the development, licensure, and introduction of a meningococcal group A conjugate vaccine in sub-Saharan Africa. The project ran from 2001 to 2014 and resulted in WHO prequalification of two polysaccharide-tetanus toxoid conjugate products, a 10 mcg vaccine for 1-29 year-olds and a 5 mcg vaccine for children under 2 years of age. The vaccine was registered as MenAfriVac®. Since 2010, the 10 mcg vaccine has been used to immunize 1-29-year-olds in large vaccination campaigns.

In 2015, WHO, with the collaboration of PATH and Public Health England, coordinated the documentation and publication of the many lessons learned through the multiple steps required to develop, test and introduce MenAfriVac® vaccine as a collection of 30 open-

access papers in a supplement of the peer-reviewed journal Clinical Infectious Diseases[15]. This collection of papers reports on the conduct of a dedicated project designed to solve an important public health problem in some of the poorest developing countries in the World. The success of the project highlights the potential of public-private partnerships to solve important public health problems, and will inform similar public health initiatives in future.

At least two further steps are required to ensure full control of group A meningitis in Africa. The incorporation of MenAfriVac® into national immunization schedules in Africa is essential to ensure that future cohorts of newborns are protected so that the public health benefits are enjoyed by future generations. Secondly, meningitis surveillance in sub-Saharan Africa must be strengthened in order to monitor the epidemiology of non-group-A meningococcal strains in Africa which could theoretically fill the ecological niche that group A used to occupy and assume epidemic proportions. This new vaccine's success has generated confidence that, over time, and with the development and use of affordable polyvalent meningococcal conjugate vaccines, meningococcal disease may well be eliminated from sub-Saharan Africa.

[15] http://cid.oxfordjournals.org/content/61/suppl_5.toc

World Health Organization

SIXTY-NINTH WORLD HEALTH ASSEMBLY **A69/34**
Provisional agenda item 15.2 **11 March 2016**

Global vaccine action plan

Report by the Secretariat

1. The Executive Board, at its 138th session, noted an earlier version of this report.[1] The report has been amended to take account of the requests by Board members for additional information on progress made to date in implementing resolution WHA68.6 (2015) on the global vaccine action plan.

2. In May 2012, the Sixty-fifth World Health Assembly endorsed the global vaccine action plan[2] 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.[3]

3. In May 2013, the Sixty-sixth World Health Assembly noted the report by the Secretariat,[4] 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.[5]

4. In accordance with the monitoring, evaluation and accountability process,[6] 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 2014,[7] and prepared the 2015 Assessment Report of the Global Vaccine Action Plan.[8]

5. A summary of the 2015 Assessment Report by the Strategic Advisory Group of Experts on immunization is included in Annex 1.

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[1] See document EB138/32 and the summary records of the Executive Board at its 138th session, ninth and tenth meetings, (document EB138/2016/REC/2).

[2] The global vaccine action plan is available at: http://www.who.int/immunization/global_vaccine_action_plan/en/ (accessed on 10 March 2016).

[3] See resolution WHA65.17 (2012).

[4] Document A66/19.

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

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

[7] The Global Vaccine Action Plan Monitoring, Evaluation and Accountability: Secretariat Annual Report 2015 is available at: http://www.who.int/immunization/global_vaccine_action_plan/gvap_secretariat_report_2015.pdf?ua=1 (accessed on 10 March 2016).

[8] The 2015 Assessment Report of the Global Vaccine Action Plan is available at: http://www.who.int/immunization/global_vaccine_action_plan/sage_assessment_reports/en/ (accessed on 10 March 2016).

6. Between March and October 2015, the Strategic Advisory Group of Experts on immunization reviewed progress made in the implementation of the global vaccine action plan. As the data taken into consideration were those available prior to the period under review, the review did not cover progress made in the implementation of resolution WHA68.6, which was adopted in May 2015 by the Sixty-eighth World Health Assembly. A preliminary report summarizing progress made to date in the implementation of that resolution is provided in Annex 2 to the present report. The final report, duly reviewed by the Strategic Advisory Group of Experts on immunization, will be included in the Secretariat's next report on progress towards the achievement of the global vaccine action plan targets.

7. Resolution WHA68.6 was adopted by Member States in response to the fact that limited access to an affordable and timely supply of vaccines is a major barrier to sustainable immunization programmes. WHO has been conducting a range of activities to increase the availability of an affordable and timely supply of vaccines, including activities to: promote vaccine research and development in developing countries; facilitate technology transfer; revise the prequalification process; streamline in-country registration procedures; strengthen procurement processes; promote price transparency; and provide information and technical support to identify the determinants of vaccine shortages. Annex 2 provides a detailed description of these efforts. Nevertheless, it should be noted that the resources available for this work are very limited and unpredictable, preventing a more systematic and comprehensive approach.

8. In April 2015, the Strategic Advisory Group of Experts on immunization endorsed a shared partner strategy to enhance sustainable access to vaccines in middle-income countries. This strategy proposes a comprehensive approach to addressing the challenges identified by countries in implementing sustainable immunization programmes, particularly with regard to access to supply.

9. It should be noted that supply-side interventions should be matched with demand-consolidation activities relating in particular to strengthening national decision-making and the national financing of immunization programmes. Furthermore, immunization should be considered as one part of a package of interventions for health care delivery aimed at preventing, protecting against and treating diseases. Such an integrated approach has already been taken for the prevention of maternal and neonatal tetanus and in the integrated global action plan for the prevention and control of pneumonia and diarrhoea.[1]

ACTION BY THE HEALTH ASSEMBLY

10. The Health Assembly 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.

[1] See http://www.who.int/woman_child_accountability/news/gappd_2013/en/ (accessed on 23 February 2016).

ANNEX 1

A SUMMARY OF THE 2015 ASSESSMENT REPORT OF THE GLOBAL VACCINE ACTION PLAN BY THE STRATEGIC ADVISORY GROUP OF EXPERTS ON IMMUNIZATION[1]

1. The Global Vaccine Action Plan (GVAP) set ambitious but achievable goals, to save thousands of lives through vaccination in this Decade of Vaccines to 2020. However The Decade of Vaccines is not on course to achieve its true potential.

2. Performance against key immunization targets remains off-track, though there have been some success stories. These isolated improvements in countries and at the global level as highlighted below will have to become the norm if the plan is to get back on track.

- The GVAP target for introduction of new or under-utilized vaccines is on track worldwide, with 86 low and middle-income countries introducing a total of 128 vaccines since 2010.
- The Ebola candidate vaccines were developed and tested within a short timeframe and showed the potential to protect against a high mortality disease.
- Following the resolution by the World Health Assembly on vaccine pricing,[2] the WHO secretariat has worked with countries to share pricing data. To date, 40 countries have shared information with WHO compared with only one country last year.
- India has been declared free of maternal and neonatal tetanus, demonstrating that it is possible to eliminate this disease even in challenging circumstances.
- Africa has not had a case of wild poliovirus since August 2014 – an enormous achievement. Nigeria is no longer a polio-endemic country.
- Polio resources were utilized in containing the outbreak of Ebola virus in Africa.
- The Americas became the first region to eliminate rubella and congenital rubella syndrome, a major achievement.

3. This assessment report focuses on the need for leadership and accountability systems at all levels, particularly within countries to put progress with the GVAP back on track.

4. Based on countries' achievements, the following common factors that would lead to success are highlighted: improving quality and use of data; community involvement; improved access to immunization services for the marginalized and displaced populations; strengthening health systems; securing and sustained supply of vaccines at all levels; leadership and accountability.

[1] http://www.who.int/immunization/global_vaccine_action_plan/sage_assessment_reports/en/ (accessed on 10 March 2016).

[2] http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R6-en.pdf (accessed on 10 March 2016).

5. At this critical midpoint of the Decade of Vaccines, **SAGE makes nine recommendations**, focusing squarely on the major issues.

To improve accountability to achieve the GVAP goals, SAGE recommends that:

– Countries have annual plans for immunization consistent with the GVAP and relevant regional vaccine action plans. The Ministries of Health, Finance and other pertinent ministries demonstrate leadership by establishing an annual process for monitoring and accountability at national and subnational levels. Monitoring should be through an independent body, for example the National Immunization Technical Advisory Group (NITAG). Each country should share, every year, with WHO regional offices, its monitoring report which should include monitoring progress towards achievement of outcomes but also sharing of best practices.

– Once regional vaccine action plans are finalised (by December 2015), WHO regional offices establish a process of annual progress review through their regional technical advisory groups and report to the respective Regional Committees. The first annual review should take place in the first half of 2016 for countries already having annual plans consistent with the GVAP. WHO Regional Committees' reports should be made available annually to SAGE as part of the global review process.

– Global, regional and national development partners align their efforts to support countries in strengthening their leadership and accountability frameworks and in implementing their national plans. This should include establishing and/or strengthening partner coordination mechanisms at each level.

– Decade of Vaccines secretariat agencies report to SAGE in 2016 on their supporting activities conducted in the 10 countries where most of the unvaccinated and under-vaccinated children live. This annual reporting mechanism should include discussion of those reports in regional technical advisory groups.

To address the shortfalls in disease-specific areas of the Global Vaccine Action Plan's implementation, SAGE recommends that:

– Given poor progress with elimination of maternal and neonatal tetanus and the relatively small funding gap to achieve this goal, WHO and UNICEF convene a meeting of global partners and the remaining 21 countries to agree on an action plan, resources and respective responsibilities so that the goal is achieved no later than 2017 and thereafter strategies are in place to sustain elimination in all countries.

– Global, regional and national development partners support countries in securing the required resources and in implementing their measles and rubella elimination or control strategies and plans. The recommendations of the mid-term review of the global measles and rubella strategic plan to be conducted in 2016, once endorsed by SAGE, should be taken into account in refining plans and for monitoring and enhancing quality of plan implementation.

To improve immunization coverage especially where many unvaccinated and under-vaccinated children live, including those affected by conflict and crisis, SAGE recommends that:

– Global, regional and country development partners should coordinate and align their efforts to support countries to immunize more children by strengthening their health-care delivery systems, combined with targeted approaches to reach children consistently missed by the routine delivery system, particularly in the countries where national vaccination rates, or subnational rates in larger countries, are below 80%, and to provide services to populations displaced due to conflict (both internally displaced persons and refugees).

– WHO should provide guidance for countries and partners on implementation of immunization programmes and immunization strategies during situations of conflict and chronic disruption.

The 2016 GVAP assessment report will also serve as a mid-term review of progress in the Decade of Vaccines and SAGE recommends that:

– This report should be presented at the World Economic Forum in Davos where the Decade of Vaccines was launched. The 2016 report should also aim to highlight those activities that were game-changers at global, regional and country levels.

ANNEX 2

ACTIVITIES BEING CONDUCTED BY WHO TO ADDRESS THE CHALLENGES COUNTRIES ARE FACING IN RESPECT OF ACCESS TO VACCINE SUPPLIES

1. VACCINE RESEARCH AND DEVELOPMENT IN DEVELOPING COUNTRIES

1. The global vaccine action plan's monitoring, evaluation and accountability framework reviews research capacity in low- and middle-income countries in each region on a biennial basis. The Secretariat's 2014 progress report on the action plan[1] includes data on the number of registered vaccine clinical trials by region.

2. In 2015, WHO convened a broad coalition of experts to develop a research and development blueprint for action to prevent epidemics.[2] The blueprint presents options for reducing the time lag between the identification of a nascent outbreak and the approval of the most advanced products that can be used to save lives and prevent the escalation of crises. Its third workstream, on global coordination and expansion of capacity, includes activities to increase the involvement of low- and middle income countries in vaccine research and development.

3. The development processes for vaccines that specifically target diseases prevalent in developing countries, such as malaria, epidemic meningococcal A meningitis and Ebola virus disease, have been taken as an opportunity to strengthen research and development capacities in low and middle-income countries.

2. TECHNOLOGY TRANSFER

4. WHO has been providing technical and financial support and facilitating technology transfer to 14 countries since 2006 to establish or enhance their capacity to produce influenza vaccines. These countries are Brazil, China, Egypt, India, Indonesia, Islamic Republic of Iran, Kazakhstan, Republic of Korea, Mexico, Romania, Serbia, South Africa, Thailand and Viet Nam. Five manufacturers have achieved licensure of their influenza vaccines as a result of this support. For the period 2015–2016, support is being focused on helping those manufacturers with influenza vaccines that are already at the clinical development stage to advance towards licensure, as well as on providing the adjuvant technology to allow for the development of dose-sparing strategies for pandemic response. As a result of these activities, it is anticipated that, by the end of 2016, this support will have resulted in an increase in global pandemic influenza vaccine capacity of at least 500 million doses.

5. In addition, financial and technical support has been provided to enable the establishment of the African vaccine manufacturing initiative. WHO, in collaboration with UNIDO and African vaccine manufacturers, has conducted an assessment of Africa's needs and opportunities for regional vaccine production. As a result of this assessment, a business plan for African vaccine production is being prepared.

[1] http://www.who.int/entity/immunization/global_vaccine_action_plan/gvap_secretariat_report_2014.pdf?ua=1 (accessed on 10 March 2016).

[2] http://www.who.int/csr/research-and-development/en/ (accessed on 10 March 2016).

6. In the regions, WHO, with partners, is implementing solutions to ensure technology transfer in the area of vaccines. These include the solutions described below.

– In the African Region, the Meningitis Vaccine Project – a partnership between WHO and PATH – joined forces with the Serum Institute of India and public health officials across Africa to develop an affordable, tailor-made vaccine for use against meningitis A in sub-Saharan Africa. A vaccine was developed in record time, at less than one tenth of the cost of a typical new vaccine.

– In the South-East Asia Region, WHO has been coordinating applications for the transfer of technology to Indian manufacturers for the production of an inactivated poliovirus vaccine from Sabin poliovirus seed strains.

– In the Eastern Mediterranean Region, WHO is supporting the transfer of technology for the influenza vaccine and inactivated poliovirus vaccine to Egypt and the Islamic Republic of Iran.

Other examples of successful technology transfer by partner agencies include the development of rotavirus and oral cholera vaccines in India and initiatives to develop a novel pneumococcal vaccine and a candidate rotavirus vaccine in Indonesia.

3. PREQUALIFICATION PROCESS

7. WHO prequalification provides assurance of the quality, safety and efficacy of vaccines for international procurement. Driven by the stringent quality requirements of donors and procurers, WHO prequalification offers manufacturers a well-established and robust means of accessing markets for products that meet internationally accepted quality norms and standards.

8. WHO has recently revised the prequalification process to reduce target time frames for prequalification once an application has been submitted. Accordingly, it has published a revised collaborative procedure for the registration of prequalified pharmaceutical products and vaccines, which was implemented on a pilot basis for the registration of inactivated poliovirus vaccines as part of the polio endgame strategy. In addition, WHO initiated a rotational fellowship programme to provide support to developing countries in building their regulatory capacity for vaccines.

9. Furthermore, in 2015, WHO published the emergency use assessment and listing procedure for candidate vaccines for use in the context of a public health emergency.

4. NATIONAL REGULATORY AUTHORITIES AND IN-COUNTRY REGISTRATION PROCEDURES

10. WHO has been providing direct support to Member States with the objective of ensuring the functionality of national regulatory authorities. The support is targeted at different groups of countries, taking into account the risk of having non-functional national regulatory authorities in countries producing vaccines and the potential significant impact on the global supply of vaccines. WHO has also been providing support to Member States to strengthen capacity for vaccine regulation through the in-country assessment of national regulatory authorities, the development of plans to strengthen those authorities and the monitoring of progress towards the full functionality of those authorities in vaccine-producing countries.

11. WHO has launched a project to estimate the costs of vaccine regulation for national medical authorities in target countries, identify appropriate fee systems in the regulation of vaccines and improve the financial sustainability of national medical authorities.

12. In the regions, WHO, with its partners, has been conducting activities focusing on specific vaccines or networks, as described below.

- The Dengue Vaccine Initiative's work includes providing technical assistance and training to national regulatory authorities (with the support of WHO) in dengue-endemic countries that have expressed interest in evaluating and licensing the candidate dengue vaccines, and carrying out an assessment of the policy environment and country readiness for the accelerated introduction of dengue vaccines in endemic countries.

- The African Vaccine Regulatory Forum, a regional network of regulators and ethicists, aims to strengthen in-country capacity for the regulation of clinical trials, including ethical approval. Its work focuses on the 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 on reviewing marketing authorization applications.

- The Developing Country Vaccine Regulators' Network is a global network of regulatory agencies from middle-income countries with fairly advanced capacity. The agencies in the network discuss concerns and the difficulties faced with regard to the evaluation of marketing authorization applications for novel vaccines, such as the dengue vaccine.

5. PROCUREMENT

13. The regional offices for the Americas, Europe and the Eastern Mediterranean have been providing support to countries on demand-consolidation activities such as demand planning and forecasting, on the harmonization of product requirements across countries and on the improvement of procurement legislation. WHO is working with the UNICEF Supply Division on the procurement of vaccines for middle-income countries.

14. As a result of efforts by the Regional Office for the Eastern Mediterranean, a number of middle-income countries have increased the procurement of routine vaccines through UNICEF. Nevertheless, because of the lack of interest from Member States, a central procurement system has not been established. The Regional Office for Europe has been working to promote the sharing of experiences on pooled procurement (for example, in the three Baltic States). Furthermore, in cooperation with the South-eastern Europe Health Network, it plans to document, in 2016, vaccine-supply challenges in upper-middle-income countries and to provide evidence-based recommendations regarding areas of action, including a review of the potential for setting up a joint procurement mechanism for the member countries of the Network. ASEAN, under the guidance of the National Vaccine Institute in Bangkok, together with the Regional Office for South-East Asia and the Regional Office for the Western Pacific, has organized two workshops on opportunities for vaccine security, an issue that is in the process of being included in the ASEAN post-2015 health development agenda. In 2015, the Revolving Fund of the Pan American Health Organization procured, on behalf of 42 countries and territories, 53 different biological products and 21 injection devices worth US$ 545 million from 31 different manufacturers.

6. PRICE TRANSPARENCY

15. In the European Region, WHO organized a subregional workshop inviting experts in the areas of vaccine management, financing and procurement from 11 Member States to share their experience and knowledge on how to access and use vaccine price and market information to improve vaccine introduction and procurement decisions.

16. WHO's vaccine product, price and procurement web platform provides an online and publicly accessible database of vaccine price information. Forty countries are currently sharing price information through the platform. The database contains 1600 vaccine price records on almost 50 different vaccine types, making it the largest international vaccine price database. More than 4000 users accessed the website in 2015, from all over the world. However, 70 Member States, over half of which are middle-income countries, have not yet shared information on vaccine prices.

7. VACCINE SHORTAGES

17. In response to concerns raised by Member States and by the Strategic Advisory Group of Experts on immunization with regard to global vaccine shortages, including shortages of traditional vaccines, WHO is facilitating an information session on pre-empting and responding to vaccine supply shortages, to be held at the April 2016 meeting of the Strategic Advisory Group of Experts on immunization.

18. In many countries, WHO has provided specific technical support to identify the determinants of vaccine shortages. For example, the Regional Office for the Western Pacific has organized meetings with the Philippines Department of Health and Department of Finance and UNICEF to analyse chronic vaccine stock outs.

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WHO'S VISION AND MISSION IN IMMUNIZATION AND VACCINES 2015–2030

World Health Organization

WHO'S VISION AND MISSION IN IMMUNIZATION AND VACCINES 2015–2030

PREVENT DISEASE.
AVERT DEATHS.
PROMOTE HEALTH.

World Health Organization

World Health Organization

DEAR WHO STAFF AND PARTNERS,

WHO's Vision and Mission in Immunization and Vaccines 2015-2030 describes WHO's strategic focus and key roles in achieving the goals of the of the Global Vaccine Action Plan 2011-2020, across all areas of work and all levels of the organization, in this decade of vaccines to 2020 and continuing to 2030.

The strategic directions described in this document are consistent with WHO reform and aligned with the Sustainable Development Goals. They reinforce WHO's longstanding role as an international leader, setting norms, establishing policies, and reaching international agreement on health priorities. They also bring forward more focused roles for WHO in providing technical assistance and managing knowledge and data.

WHO's Vision and Mission illustrates how the organization plans to evolve its critical role in immunizations and vaccines to meet the needs of future health programmes. It will be used to guide internal decisions about where to focus resources, at what level of the organization, and in which strategic directions.

WHO staff at all levels has participated in the development of this document. By sharing it with our partners and stakeholders, we hope to show how WHO will achieve its mandate over this exciting period of transition and expansion in the field of immunization.

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CONTENTS

1 PREAMBLE

Between 2010 and 2015 more than 5 million deaths[1] were averted annually thanks to vaccinations delivered around the world.

This estimate does not include the impact of rotavirus vaccine and pneumococcal vaccines, for which no estimates are available. Immunization continues to be one of the most powerful and cost-effective interventions in public health.

In the past two decades, the scope of immunization has expanded significantly as new vaccines and delivery technologies have been introduced into routine immunization programmes worldwide. The same period has witnessed a proliferation of actors in the global arena that promote immunization and help vaccines reach an ever-larger number of children, adolescents and adults. The horizon is filled with prospects of new vaccines, delivery technologies and stronger systems.

In 1974, a World Health Assembly resolution launched the Expanded Programme on Immunization (EPI) to immunize children worldwide with six vaccines. Since then, the World Health Organization (WHO) continues to act as the global authority on immunization in accordance with its constitution and obligation to its 194 Member States. In an increasingly interdependent global environment, WHO has and will continue to focus on its core roles in immunization: to set norms and standards; convene global expertise; develop, promote, and facilitate adoption of new guidelines; and monitor national and global achievements and progress.

To further articulate how these roles will evolve over the next 15 years, WHO developed a new *Vision and Mission*

for Immunization and Vaccines for the period 2015 – 2030. This document presents the key focus areas and a series of strategic directions that define our core business for the future coinciding with the new Sustainable Development Goals era.[2]

The scope of this document includes work on immunization and vaccines taking place across all levels of WHO. A new articulation of WHO's mission, vision and strategic directions will enable the organization to better anticipate and respond to the opportunities and challenges of the immediate future. It will position WHO with the capacity and competencies needed to fulfil its mandate and streamline its core functions at global, regional and country levels. It will assist WHO in positioning itself clearly within on-going implementation of the Global Vaccine Action Plan (GVAP)[3] and prepare itself for the decade following the GVAP: 2020 to 2030. It will also provide the basis for future global and regional plans.

This document was developed through a process that included consultations with immunization teams in all WHO regional offices and a range of meetings with other key staff in all departments engaged in vaccines and immunization work in its headquarters office in Geneva and in selected country offices. Two distinct pieces of work were undertaken to inform the work: a historical review of 40 years of EPI illustrates the main determinants for EPI successes (Annex 4) and a survey among users of WHO products and services identifies responsibilities that WHO does well and those areas that could be done equally well by partners (Annex 5). This research helped WHO identify areas where we have a unique role and comparative advantage and areas that could be phased out.

Recognizing that immunization programmes have and will continue to undergo rapid change, we shaped our mission and strategic focus areas around a set of assumptions about the environment in which immunization programmes will operate in 2030. The new environment for immunization is described on the following pages:

[1] Based on WHO estimates of deaths averted from diphtheria, tetanus, pertussis and measles and Ehreth's estimates (EhrethJ: Vaccine 21 (2003) 596 - 600) of deaths prevented from Hib, HepB, polio and TB. Additional deaths are prevented with the increasing uptake of vaccines against *Streptococcus pneumoniae* and rotavirus.

[2] Sustainable Development Goals. http://www.un.org/sustainabledevelopment/sustainable-development-goals/

[3] *Global Vaccine Action Plan 2010 - 2020*. Geneva, World Health Organization, 2012.

What will 2030 look like?[4,5]

By 2030, the immunization environment will look very different than it does today.

Countries are experiencing broad demographic and economic changes. Already, there are more people living in middle-income countries than in low-income countries. Increased economic stability will provide countries more ownership over their immunization programmes, and countries will require more specialized technical assistance to make decisions and address problems. More countries will have sufficient capacity for medicines regulation and will be less reliant on WHO's prequalification process at the global level.

The Sustainable Development Goals will have provided direction for economic and social development. Health indicators will be broader, encompassing communicable and non-communicable diseases as well as emerging burdens related to climate change, increased travel and trade, and new infectious and vector-borne diseases. Prevention will continue to be important, and attention will continue to be directed to interventions that are considered cost-effective.

More vaccines will be available to protect against more diseases throughout the human life course. Immunization will likely become part of an integrated package of disease prevention strategies, meaning that immunization services will be accompanied by other services and delivered in more places, including schools, homes, and pharmacies. New, easier-to-use immunization

delivery technologies may be more widely available, making it possible for non-health personnel to deliver immunization. Electronic devices and software systems will make data collection and analysis easier and more powerful, enabling managers and health staff to more efficiently identify and reach people previously missed by immunization and to tailor services to the most optimal delivery methods.

Disease elimination and eradication programmes will continue to exist, but as part of stronger health systems that have regular and reliable contact with communities, even those in remote and hard-to-reach areas. Routine and campaign immunization services will be managed in a single platform.

More successful immunization programmes will lead to fewer people falling ill and dying from vaccine-preventable diseases, and demand for immunization may begin to drop.

In such an environment, health priorities are expected to shift to the prevention and control of non-communicable diseases. Immunization technologies may gradually play a role in treating chronic conditions and in managing antimicrobial resistance.

Immunization services and demand for those services must be more purposefully maintained, together with strategies to understand and overcome vaccine hesitancy.

Transparency on vaccine pricing will become ever more important. Fragile states will continue to exist, and the disparity between health outcomes in stable and fragile countries may continue to increase. These countries will require ongoing support to maintain reliable immunization services amongst larger age groups and more difficult-to-access populations.

[4] *Twelfth Global Programme of Work*. Geneva, World Health Organization, 2014 (http://www.who.int/about/resources_planning/twelfth-gpw/en/, accessed 9 September 2015)

[5] Chaferhoff M, Schrade C, and Suzuki E. Analysing proposals for reform of the global health architecture. London, Chatham House Royal Institute of International Affairs, Centre on Global Health Security, 2015.

2 VISION

Our vision statement presents where we want to be in the future and the impact that we intend to have on health in the world.

OUR VISION:

The highest attainable standard of health for all individuals and communities by preventing disease.

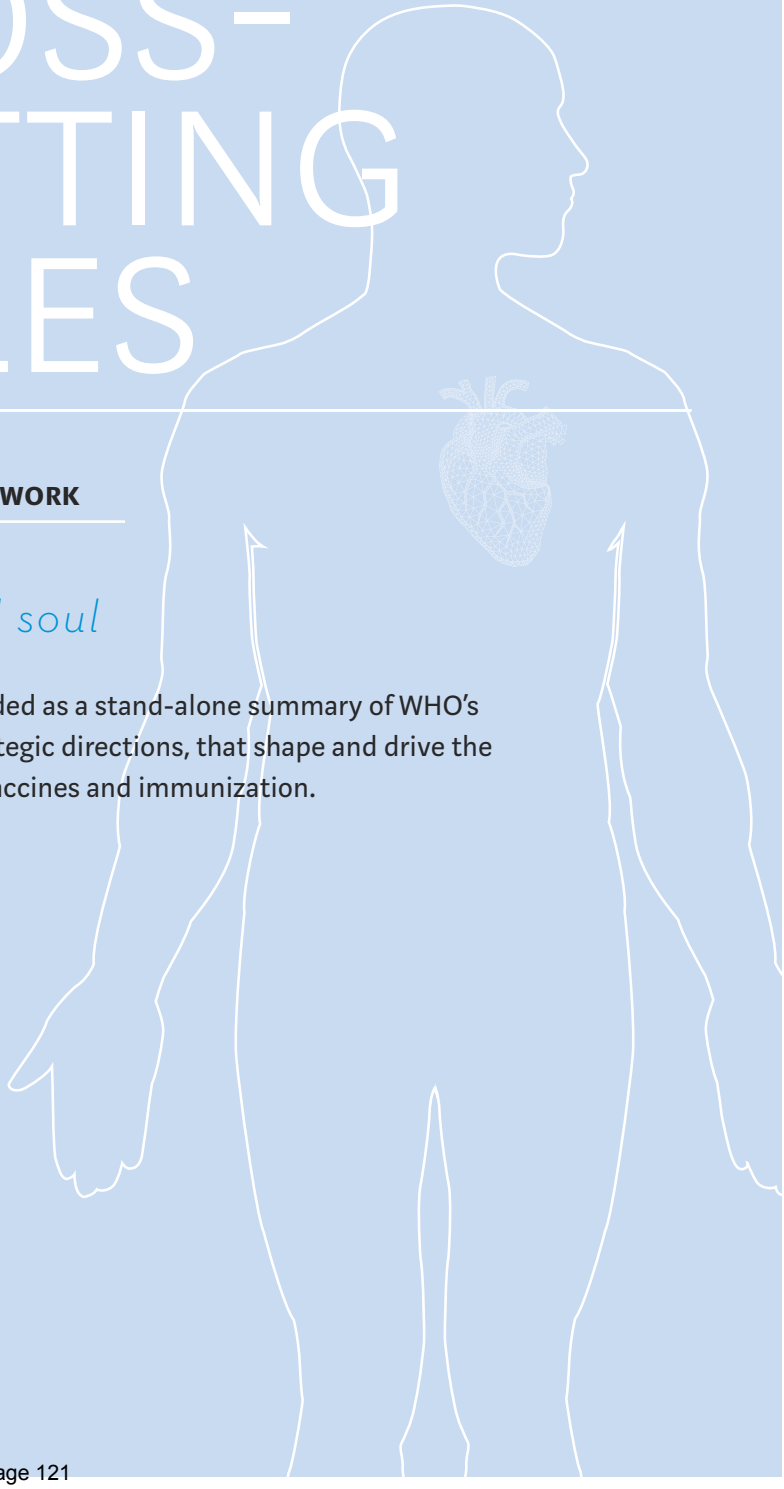
3 MISSION

Our mission statement presents the purpose and focus of our work in immunization and vaccines over the next 15 years.

OUR MISSION:

To support all countries to deliver quality immunization services as part of an integrated, people-centred platform of disease prevention that spans the human life-course.

4 WHO'S STRATEGIC FOCUS AND CROSS-CUTTING ROLES



4.1 THE STRATEGIC FRAMEWORK

Our heart and soul

This framework is intended as a stand-alone summary of WHO's mission, vision, and strategic directions, that shape and drive the organization's work in vaccines and immunization.

WHO IN IMMUNIZATION

The highest attainable standard of health for all individuals and communities through preventing disease.

OUR MISSION:

To support all countries to deliver quality immunization services as part of an integrated, people-centred platform of disease prevention that spans the human life-course.

OUR CROSS-CUTTING ROLES:

Proactively share information across all areas

OUR STRATEGIC FOCUS:

Vaccines

Encourage and support research that is used to inform norms and standards. Identify necessary regulatory pathways to accelerate the development, licensure and introduction of new vaccines and related technologies and strategies.

STRATEGIC DIRECTIONS:

1. Promote the development of new vaccines and vaccine delivery technologies to meet public health priorities
2. Establish norms and standards for vaccines and delivery technologies
3. Ensure vaccines and delivery technologies are of assured quality

Immunization

Collect and share evidence that countries use to inform their choice of strategies to ensure that vaccines are available, affordable and accessible to all.

STRATEGIC DIRECTIONS:

1. Support national immunization systems to become more effective and efficient
2. Monitor and analyse global, regional and national immunization data
3. Ensure the sustainability of immunization programmes
4. Apply social and behavioural sciences to immunization
5. Sustain immunization services in emergencies
6. Lead and coordinate disease elimination and eradication efforts

PRINCIPLES ALIGNING HOW WE WORK:

ACCOUNTABLE	COUNTRY-LED
INTERCONNECTED AND INTERDEPENDENT	
EFFICIENCY-DRIVEN	IMPACT-ORIENTED

4.2 THE STRATEGIC DIRECTIONS

Our mind and body

Our strategic directions look both upstream at the development and regulation of vaccination and delivery technologies and downstream at the implementation of immunization services. Each of these areas were selected based on consultation across WHO regional and headquarters (HQ) offices, with input from selected country offices, which have determined our nine strategic directions through 2030.

For each strategic direction a specific approach has been defined with a view toward where we expect to be in 2030. These strategic directions and approaches are presented in Annex 1.

4.3 ROLES THAT CUT ACROSS ALL AREAS OF WORK

Our brain

As we look to the future, we recognize the areas of work where WHO is already acknowledged—both internally and by partners—as playing a critical role across technical streams. Regardless of the area of immunization—e.g., measles elimination, outbreak response, new delivery technologies or supporting national immunization systems to become more effective and efficient—WHO's leadership in these cross-cutting roles is and will remain necessary and consistent. We also identify a few expanded roles that WHO considers both vital and important—these include adopting broader strategies for disease prevention and increasing our capacity to collect and analyse data.

The cross-cutting roles presented below describe how WHO will work over the next 15 years.

CONVENE LEADERS AND EXPERTS FROM ALL SECTORS.

WHO's role in convening experts in immunization is well established and globally critical. Whether it is to convene ministries of health and immunization managers to discuss regional issues, getting all partners within the country to meet and agree on implementation plans, or bringing together global experts across a range of disciplines to recommend evidence based policy, WHO is recognized as a trusted convener at national, regional and global levels.

ESTABLISH STANDARDS FOR PRODUCTS AND TECHNOLOGIES.

WHO's normative role and standard-setting for vaccines, biologicals and technologies is relied upon by countries, private companies, United Nations (UN) agencies and partners to ensure that immunization products are effective, safe and suitable for all people around the world. WHO is recognized as a neutral broker and thus has a unique role to play in this sphere that is not—and some argue cannot—be filled by others.

DEVELOP EVIDENCE-BASED POLICY RECOMMENDATIONS AND GUIDANCE.

WHO's role in establishing policy recommendations and guidance across all areas of immunization—from data collection to new vaccine introduction to stockpile management—remains critical for maintaining equitable, efficient and consistent immunization programmes around the world. Countries routinely look at WHO policy recommendations and guidance when developing their own strategies, programmes and implementation plans. Expert groups such as the Strategic Advisory Group of Experts on immunization (SAGE) are particularly important, as partners in bilateral agencies, foundations, and private companies refer to SAGE recommendations when planning their immunization services support and products. Similarly, the work of regional technical advisory groups is crucial to tailor policy to the specific needs and contexts of each WHO region.

→ FACILITATE SYNERGIES FOR DISEASE PREVENTION AND CONTROL.

WHO will increasingly play a key role in helping countries meet international norms, implement national health plans and identify synergies across health services that can result in more effective and efficient health systems. WHO will also play a role in linking immunization with other health agendas, such as emerging diseases, antimicrobial resistance, and new disease control objectives. Providing technical guidance on programme implementation is also a critical role that WHO will increasingly address from the regional and country level.

→ MONITOR AND USE DATA FOR ANALYTICS.

With support from Member States, academic partners and national institutes, WHO provides a nexus for the consolidation, analysis, and dissemination of data and information across all immunization and vaccine preventable disease areas. WHO will continue to assess data for quality and reliability so it can be used to inform priorities, activities and plans, and support decision-making processes at all levels. As electronic information systems begin to proliferate in developing country health systems, WHO will work with countries to extract the most useful data that can be used to make decisions and inform health strategies at all levels. WHO will also use state-of-the-art analytics and data visualization technologies to analyse data and use it to prioritize investments and develop new prevention goals.

4.4 RESPONSIBILITIES OF EACH LEVEL OF THE ORGANIZATION

Our arms and legs

Over the period 2015 to 2030, there will be a gradual shift in the critical roles of the different levels of the organization. The overall intention is to narrow the focus of HQ to areas where a global approach is required and strengthen and enhance the roles of the regional and country offices.

The table on the next page illustrates the major roles that the global, regional, and country-level WHO offices will play. More information on the division of responsibilities is provided in Annex 2.

TABLE 1. SOME EXAMPLES OF KEY ROLES WHERE WE EXPECT A SHIFT FOR THE ORGANIZATION

CORE ROLE	HQ	REGIONAL OFFICE	COUNTRY OFFICE
Convene leaders and experts from all sectors	More actively involve Civil Society Organizations in setting policies and monitoring their implementation.		
Establish norms and standards for products and technologies	Promote the harmonization of international norms and standards, and assist regions in developing and implementing policies to guide the regulation of all health products including vaccines.	Help strengthen national regulatory agencies or regional regulatory mechanisms to progressively reduce the need for prequalification systems.	Guide WHO regions and headquarters in efforts to monitor the roadmap for vaccine pre-qualification and regulatory authority Institutional Development Plans.
Develop evidence-based policies and guidance	Develop social and behavioural strategies to address hesitancy and demand.	Help tailor global strategies and support their regional implementation.	Support countries to establish their own national policies and strategies related to immunization and disease control and prevention.
Facilitate synergies for disease prevention and control	Identify opportunities for collaboration across health programmes to improve disease prevention and control efforts.	Facilitate inter-country and inter-regional coordination and collaboration on immunization and elimination and control of vaccine-preventable diseases.	
		Support countries and partners' internal and external fundraising efforts, and align external assistance with country needs and priorities.	
Monitor and use data for analytics	Enable better internal and external global decision-making by sharing the best available global immunization data using analytics and visualizations.	Support inter-country collaboration to obtain quality data and conduct regional immunization and disease risk analyses.	Promote the use of new ideas and technologies (including information and communications technologies) to make data collection and use more effective, accurate and efficient.

5 PRINCIPLES ALIGNING HOW WE WORK

Our pulse

WHO has identified five principles to guide our decisions and actions through 2030. These principles are relevant at both an individual and collective level and are meant to facilitate a shared understanding of WHO's interests and goals at each level of the organization. We expect these principles to translate into behaviours that define a common culture for how those who work in vaccines and immunization at WHO approach our work and how we relate to colleagues and partners.

Our principles are aligned with the WHO reform and thus in step with on-going programmatic and managerial changes at WHO.[6] For example, the WHO reform has a stronger country-focus and introduces more rotation and mobility for human resources, which will strengthen regional and country capacity and facilitate more interaction between all levels of the organization. It will thus enhance several of the principles described on the next page.

6 *Our Reform Story*. Geneva, World Health Organization, 2013 (http://www.who.int/about/who_reform/change_at_who/strategic_vision/en/#.VfBavnjiLU4, accessed 9 September 2015).

1 ACCOUNTABLE

- Acknowledge and take responsibility for meeting our objectives and commitments by setting and enforcing clear expectations at all levels
- Maintain high ethical and professional standards by asserting an evidence-based and independent perspective

2 COUNTRY-LED

- Follow governments' lead and help them take ownership of their decisions and plans
- Invite country participation in regional- and global-level dialogue
- Cultivate and reinforce country-level capacity to sustain immunization achievements

3 INTERCONNECTED AND INTERDEPENDENT

- Seek and foster synergies across health areas that have the potential to optimize outcomes
- Strengthen internal and external collaborations that can speed or enhance outcomes

4 EFFICIENCY-DRIVEN

- Work efficiently, i.e., seek maximum results from limited resources
- Provide timely access to data and information so that all actors can react and work quickly
- Streamline processes that make it easier to collaborate with internal and external colleagues

5 IMPACT-ORIENTED

- Draw attention to new issues, encourage ongoing learning and innovation, and actively promote successful ideas and initiatives
- Set priorities and allocate resources in alignment with the delivery of results
- Improve programme performance, so that everyone who needs vaccines has reliable access
- Promote equity in immunization

6 THE ROLE OF WHO WITH ITS PARTNERS

Our family

WHO has always worked closely with partners to set norms and standards, provide direct guidance and seek financial support for Member States. Without the ideas and contributions of partners, none of last decade's successes in immunization would have been possible.

Since the EPI launched in 1974, the number and type of partners involved in immunization has increased dramatically (see Annex 3). WHO partners in immunization include: the countries themselves (Ministry of Health, other Ministries, technical agencies), financial partners, manufacturers, UN agencies, international technical agencies, bilateral agencies and projects, and civil society organizations.

In this section, we illustrate the many ways in which WHO works with partners to help achieve our Vision and Mission in Immunization and Vaccines between now and 2030.

1. *Financial partners*

Foundations, official development agencies, and Gavi, the Vaccine Alliance have been providing financial and technical support to both countries and WHO allowing great achievements in morbidity and mortality reduction over the past decades. Ongoing support from donors complemented by increasing spending from countries themselves will ensure that recent achievements are sustained and that programmes will continue to improve in all countries.

WHO WILL SUPPORT THE WORK OF FINANCIAL PARTNERS BY:

- Highlighting areas where financial and technical support is most needed
- Providing technical support to countries and defining norms, standards, policies and strategies for immunization
- Monitoring and evaluating national, regional and global programmes and strategies for immunization

2. *Manufacturers*

Providing adequate quantities of efficacious, safe and cost-effective vaccines and equipment is a prerequisite for strong programmes and an essential element in strengthening health security. Manufacturers of vaccines and immunization technologies, including those in low- and middle-income countries, are key partners for providing quality vaccines and other immunization technologies to countries.

WHO WILL SUPPORT THE WORK OF MANUFACTURERS BY:

- Providing guidance on how current and future vaccines and immunization technologies can be adapted to fit the needs and constraints of low-resource settings
- Developing country capacity to regulate vaccine safety and efficacy and harmonize regulatory requirements across regions
- Helping countries more accurately forecast vaccine needs and mobilize the resources required to purchase vaccines

3. United Nations agencies and global initiatives

Many UN agencies and global initiatives include immunization activities in their purview. Their collaboration is crucial to ensure that immunization is integrated across all strategies and programmes and, inversely, that immunization is a useful complement to ensure successful implementation of other health interventions.

WHO will support the work of other UN agencies and global initiatives by:

- Integrating related health and other development strategies into immunization programmes, where possible
- Improving health systems so that other health interventions benefit from strong immunization programmes
- Coordinating with other UN agencies and global initiatives to provide technical and financial support to countries
- Coordinating the production and use of accurate and complete data

4. Technical partners

The category "technical partners" covers a range of different institutions: national and international technical agencies and non-governmental organizations, universities and research institutes, scientific societies, and individual consultants and consulting companies.

Some of these institutions have been granted the status of WHO Collaborating Centres. This status, granted after several years of strong partnership, reinforces the link between institutions and provides stronger alignment between WHO objectives and the collaborating centres' activities.

WHO will support the work of technical partners by:

- Drawing upon their expertise and knowledge when developing WHO norms, standards and policies
- Validating and sharing monitoring and evaluation data collected from national, regional and global immunization programmes

5. *Civil Society Organizations (CSOs)*

Historically, the relationship between WHO EPI and civil society, including CSOs, has been relatively weak. However, civil society organizations have been increasing their involvement and support of immunization programmes worldwide and both WHO and CSOs stand to benefit from stronger collaboration and cooperation. Whereas WHO plays a leading advisory role to country governments, CSOs are often the immunization stakeholders closest to communities and populations.

As CSOs continue to expand their interest in immunization, particularly in relation to the GVAP implementation, WHO will proactively engage with CSOs and help them advocate for vaccines and immunization, support Member States and remain relevant and evolving players in global health.

WHO WILL SUPPORT THE WORK OF CIVIL SOCIETY BY:

- Involving civil society representatives as full participants in immunization programme planning, implementation, monitoring and reporting, and meetings and events.
- Facilitating the relationships between government and civil society with regards to immunization

ANNEX 1

STRATEGIC AREAS AND DIRECTIONS

STRATEGIC AREA: *Vaccines*

1.1 STRATEGIC DIRECTION: PROMOTE THE DEVELOPMENT OF NEW VACCINES AND VACCINE DELIVERY TECHNOLOGIES TO MEET PUBLIC HEALTH PRIORITIES

Research and development (R&D) for new and improved vaccines and vaccine delivery technologies is central to all efforts to prevent diseases with significant morbidity, mortality and economic burden, especially in low and middle-income countries.

WHO has been involved in vaccine and delivery technology R&D for many years, facilitating productive dialogue with manufacturers and helping research institutes and manufacturers prioritize R&D investments. Over the next 15 years, WHO will continue to work with manufacturers and research institutes to recommend vaccine R&D priorities and foster the development of new technologies that can be used to meet public health priorities, such as thermostable, community-provided vaccines and needle free delivery devices.

APPROACH:

- Develop global agendas for R&D, set in collaboration with expert groups, around vaccines and delivery technologies that address public health priorities of low and middle-income countries and formulate new research needs and promote the development of research partnerships.
- Help define target attributes and development pathways for novel vaccines/combinations and delivery technologies using preferred product characteristics (PPCs) and other guidance documents to address future implementation challenges.
- Create streamlined and accelerated development pathways for vaccines and delivery technologies by: encouraging collaboration among research centres and WHO collaborating centres, including those located in low and middle-income countries; facilitating technical support for research projects; providing expert advice on intellectual property, and facilitating technology transfer, when appropriate.
- Support vaccine development where no vaccine exists and the development of new technologies for epidemic outbreak responses and disasters. This would include efforts to facilitate the development of vaccines for use in emergency settings, for example, through the design of decision-making frameworks, epidemiological risk assessments, and guidance on vaccine characteristics and implementation considerations.

1.2 STRATEGIC DIRECTION: ESTABLISH NORMS AND STANDARDS FOR VACCINES AND DELIVERY TECHNOLOGIES

One of WHO's core roles is to establish and promote global norms and standards for medicines and devices that safeguard the quality, safety and efficacy of vaccines and delivery technologies, but also help to streamline regulatory processes, and remove obstacles to product evaluation and registration. WHO also works with countries to translate global norms and standards into regional and national regulatory practice. In 2014, the portfolio of WHO standards for biological substances extended to over 70 written standards and 300 international biological reference preparations.

Over the next 15 years, as countries begin to take on more regulatory responsibility for medicines and devices, WHO will promote regulatory convergence of international norms and standards. WHO will also seek to improve its norms and standards process so it can quickly assimilate scientific advances in production and control of vaccines and devices into the normative process.

APPROACH:

- Convene expert committees and promote international laboratory collaborations to set norms, standards and reference preparations and develop standards for new vaccine candidates.
- Promote the use of internationally-agreed norms and standards among all relevant international and national actors.
- Achieve convergence of international norms and standards in support of a globalized supply chain.
- Monitor scientific advances in vaccine and delivery technology production and control and translate them into evolving norms and standards.

1.3 STRATEGIC DIRECTION: ENSURE VACCINES AND DELIVERY TECHNOLOGIES ARE OF ASSURED QUALITY

Prequalification is a process established to ensure that vaccines and delivery technologies purchased by UN procurement agencies are consistently safe and effective under conditions of use by national immunization programmes. As national regulatory authorities become stronger and increasingly align their procedures with those of stringent National Regulatory Authorities (NRAs) or regional regulatory mechanisms, WHO expects that the need for the prequalification systems will gradually reduce to be used only in exceptional circumstances.

In an effort to build sufficient regulatory capacity in countries, WHO will continue to work with regional and national regulatory bodies to implement globally-accepted norms and standards so that all countries have access to safe, effective and high-quality vaccines and delivery devices.

APPROACH:

- Guide the development of stronger national regulatory systems.
- Expedite the registration of vaccines and devices.
- Convene expert committees to assess the degree to which vaccines and delivery technologies meet the needs of recipient countries
- Promote post-marketing surveillance of delivery technologies and vaccines to inform decision-making and any revisions to product specifications.

STRATEGIC AREA:	*Immunization*

2.1 STRATEGIC DIRECTION: SUPPORT NATIONAL IMMUNIZATION SYSTEMS TO CONTINUOUSLY BECOME MORE EFFECTIVE AND EFFICIENT

WHO's central role in immunization puts it in a unique position to set ambitious global goals and galvanize national, regional and global commitment to achieve those goals. Over the next 15 years, WHO will support Member States to provide quality immunization services as part of stronger and more integrated health systems. In this context, WHO will focus less on the provision of direct technical assistance and more on establishing necessary enabling functions that empower Member States to strengthen their own national systems.

APPROACH:

Seek political commitment for immunization through legislative and policy changes.

- » Gain appropriate political commitment from WHO Member States to prioritize immunization and establish common global and regional vaccine-preventable disease (VPD) control goals.
- » Facilitate inter-country and inter-regional coordination on immunization and VPD elimination and control.
- » Promote in-country legislation that secures budget lines for vaccines and immunization, requires checking immunization for school entry, and facilitates the equitable and universal access to and use of immunization services in the context of the country's health system (e.g., mandates for free-of-cost vaccination, mandates for reporting vaccination data from all sectors, etc.).

Provide strategic and practical guidance to countries.

- » Convene multidisciplinary global and regional advisory bodies to formulate recommendations and provide guidance on immunization policies, strategies and practices.
- » Establish and strengthen national bodies such as National Immunization Technical Advisory Groups (NITAGs) and NRAs to promote and facilitate in-country decision-making and oversight.
- » Set the global and regional agenda for, and facilitate the implementation of operational and economic research to inform decisions on disease prevention, and more effective and efficient immunization services.
- » Develop frameworks and portals with the latest evidence and tools to evaluate diseases and the economic impact of immunization.
- » Promote life course approaches to immunization and integrate vaccination activities with broader disease-prevention efforts.

Support programme planning, budgeting and financing.

- » Support the development of strategic multiyear and annual operational plans that respond to programme evaluations and are aligned with government budget cycles.
- » Support Member States, as requested, with internal and external advocacy, communications, and fundraising efforts, and help align external support to country needs and priorities.
- » Support Member States with planning and costing of operational activities for nationwide scale up of new vaccines, including those outside the traditional EPI system.

Involve new actors and introduce new technologies to improve implementation.

- » Involve civil society and other actors in government-led health planning and in health system strengthening to promote equity and universal access to immunization.
- » Use workforce development and the adoption of new technologies, systems, and practices to support monitoring, evaluation and improvement of supply chains, service delivery, micro-planning, and in-country financial flows.

Provide guidance and tools to help countries with monitoring and evaluation, disease surveillance and Adverse Events Following Immunization.

- » Support countries to establish appropriate, externally accredited surveillance laboratories and surveillance systems that provide information on the burden and epidemiology of VPDs.
- » Increase the use of immunization and surveillance data to monitor immunization system performance and inform strategic, managerial, and operational decisions at national, subnational and local levels.
- » Support countries to establish and/or strengthen pharmacovigilance systems to detect, investigate and respond to Adverse Events Following Immunization (AEFI) and improve vaccine safety.
- » Promote the use of new ideas and technologies (including information and communications technologies, or ICT) that improve the accuracy, efficiency, and effectiveness of data collection and use.

2.2 STRATEGIC DIRECTION: MONITOR AND ANALYSE GLOBAL, REGIONAL AND NATIONAL IMMUNIZATION DATA

The collection, analysis, and use of data to monitor and evaluate national immunization programme performance from a global and regional perspective is a priority for WHO, its Member States, and immunization partners. Data analysis is also crucial for WHO and its partners to establish global, regional and national immunization policies and to monitor progress towards achievement of their objectives.

Over the next 15 years, WHO will continue to collect and validate coverage and vaccine management data to monitor programme performance and identify issues countries are facing. Data from surveillance systems (including disease incidence and AEFI rates) will also be used to develop immunization policies that are evidence-based and tailored to countries' needs.

APPROACH:

- Remain the prime source of immunization data and analytics at national, regional and global levels.
- Use innovative technologies to collect, interpret, share and use data in real time, while minimizing the reporting burden for Member States.
- Gather immunization data from all levels in a single global repository that WHO and partners can use to develop evidence-based global, regional and national immunization policies.
- Support better internal and external decision-making by disseminating accurate and timely immunization data and by using state-of-the-art analytics and visualizations.

2.3 STRATEGIC DIRECTION: ENSURE THE SUSTAINABILITY OF IMMUNIZATION PROGRAMMES

As the economic status of countries improves, more middle-income countries have begun to assume responsibility for their immunization programmes without or with very limited external financial resources. To date, donors and partners have provided investments to offset the cost of purchasing and implementing new vaccines and achieving more ambitious goals, however national governments with sufficient economic means are expected to maintain much larger and more complex immunization programmes over the long-term.

Over the next 15 years, WHO will coordinate with key immunization partners to help these countries achieve stronger and more sustainable immunization programmes by focusing on four key areas: enhanced decision-making capacity for immunization, increased political commitment, increased demand for immunization services and more timely access to affordable vaccine supply.

APPROACH:

- Support countries to make timely, evidence-based decisions about vaccine policy and programme choices by building internal capacity to generate evidence and strengthening national decision-making mechanisms (such as NITAGs).
- Help countries build stronger political and legislative support for immunization programmes and secure more dependable domestic financing, by demonstrating the broader socio-economic value of vaccines.
- Work with countries to improve both the reliable and timely supply of vaccines to immunization delivery points and maintain high demand for immunization services from the community.
- Improve vaccine price transparency and address major barriers that limit countries' access to affordable and timely supply of vaccine.

2.4 STRATEGIC DIRECTION: APPLY SOCIAL AND BEHAVIOURAL SCIENCES TO IMMUNIZATION

In the last 40 years, most of WHO's concentration has focused on vaccine technologies and the many components required for effective service delivery, detailed planning and costing, skilled managers and vaccinators, and monitoring systems.

We are learning that while infrastructure and technologies are indeed important to the success of immunization programmes, the actors involved in immunization (i.e., caregivers, community and religious leaders, health workers, logisticians, and decision-makers) and their knowledge, behaviours, and interactions are vital to achieving our immunization goals.

Despite increased recognition of the importance of these actors' roles and responsibilities, it is less clear how to facilitate and enhance their different forms of participation, especially given the interconnected exchanges between the various actors and their social context.

A field of research and practice in this area is beginning to open with new work streams emerging around vaccine hesitancy and demand generation. At the same time, we have yet to understand how behaviours, their determinants, and their connectedness collectively influence the programme outcomes we have been monitoring for decades.

A challenge remains in wholly understanding how behaviours with respect to vaccination are shaped by both constant and changing factors in the social environment. Our focus will include an exploration of the links between the health system, frontline service providers, and the individuals and communities they serve, including factors that determine vaccine uptake such as trust and complacency. Moreover, our approach will be systematic and cross-cutting with the intent to establish a new area of technical expertise in the social and behavioural sciences to optimize immunization programmes.

APPROACH:

- Coordinate with independent expert groups to set a research agenda, synthesize and disseminate the evidence, monitor advances and manage the knowledge base.
- Develop evidence-based processes and guidance to improve the performance of immunization programmes, through the use of implementation research, and social and behavioural sciences.
- Promote the integration of behavioural measures and indicators into routine monitoring to inform continuous learning and tailored programme implementation.

2.5 STRATEGIC DIRECTION: SUSTAIN IMMUNIZATION SERVICES IN EMERGENCIES

The need for immunizations in non-epidemic disasters is often high and specific strategies must be in place to quickly and decisively respond to such disasters.

WHO's emergency response team will provide global coordination and leadership to ensure that proven and effective vaccines are available and rapidly deployed to tackle outbreaks of diseases such as yellow fever, cholera, meningitis, Ebola, and typhoid. This effort will reduce the risk and impact of emergencies by providing efficient access to, and use of safe, effective and affordable vaccines.

APPROACH:

- Strengthen country capacity for preparedness and resilience to epidemic and non-epidemic emergencies, including the development of effective surveillance systems.
- Develop guidance on the delivery of vaccination in humanitarian emergency situations including for protracted crisis, including monitoring and evaluation guidelines.
- Ensure that appropriate vaccines are available for all potential vaccine preventable disease epidemics.
- Maintain international vaccine stockpiles for selected diseases to ensure an equitable access to sufficient vaccine quantities at an affordable cost.

STRATEGIC DIRECTION:
2.6 LEAD DISEASE ELIMINATION AND ERADICATION EFFORTS

Consistent with WHO's mission "to realize the full potential of vaccines", WHO will continue to lead efforts with key partners to eliminate Measles and Rubella, Hepatitis B and Maternal and Neonatal Tetanus and eradicate Poliomyelitis and other diseases where elimination or eradication is being endorsed as global or regional targets.

As current disease elimination and eradication efforts are achieved, WHO's role in new eradication and elimination efforts will shift from implementation to goal setting, partnership coordination, strategic development, monitoring and evaluation.

APPROACH:

- Lead and coordinate new eradication and elimination goals.
- Set and develop strategies to achieve global regional control/elimination/eradication targets.
- Provide training, technical support and staff supervision to enhance country capacity for specific eradication strategies.
- Support global networks of WHO-accredited public health laboratories that can diagnose and track virus movement and therefore drive implementation.
- Mobilize resources necessary for elimination/eradication.
- Establish and oversee implementation of global/regional certification criteria.
- Oversee the post-eradication agenda for diseases such as polio.
- Develop containment standards for biologicals once targets are achieved (for eradication).
- Develop stockpiles and guidance to respond to outbreaks post eradication.

ANNEX 2 DIVISION OF RESPONSIBILITIES BETWEEN HQ, REGIONAL, AND COUNTRY OFFICES

This section outlines the roles and responsibilities of HQ versus regions versus country office. It will be discussed and revised with input from country, regional and headquarters staff every five years.

TABLE 2. WHO CORE ROLES ENVISIONED FOR 2030 IN IMMUNIZATION AND VACCINES

	HQ	REGIONAL OFFICE	COUNTRY OFFICE
Convene leaders and experts from all sectors	Convene technical experts to guide global policies and set priorities. Secure global endorsement of key policies through the World Health Assembly. Strengthen coordination between each level of WHO and between WHO and key partners. Enhance and maintain relationships with collaborating centres, universities and academic bodies. Develop advocacy strategies and tools for global and national use.	Support Member States to engage in governing bodies. Convene regional intergovernmental meetings and working groups and establish inter-regional health platforms. Engage Member States in international initiatives and coordinate with regional and sub-regional entities on their participation in global health issues. Increase visibility of immunization and WHO's role in immunization. Hold governments accountable to implement priority immunization commitments. Strengthen capacity to present scientific evidence when communicating with policymakers and communities.	Advocate for immunization of all recommended age groups in health sector plans. Strengthen government capacity to coordinate with other ministries, private sector entities and external partners in all immunization areas. Support governments to convene and coordinate health response in emergencies. Ensure that the comprehensive multiyear plan is the guiding document for health sector planning. Advocate with governments for sufficient funding for immunization programmes.
	Actively involve Civil Society Organizations in policy setting and implementation discussions		

TABLE 2. WHO CORE ROLES ENVISIONED FOR 2030 IN IMMUNIZATION AND VACCINES, *continued*

	HQ	REGIONAL OFFICE	COUNTRY OFFICE
Establish norms and standards for products and technologies	Set norms and standards with input from technical experts, regional offices, and country-level representatives. Promote the convergence/ harmonization of international norms and standards and regulatory procedures across all countries. Foster an environment that enables countries to oversee their own implementation of norms and standards.	Adapt norms and standards to the regional context, as necessary. Monitor the implementation of norms, standards and guidelines at country level. Build country capacity to implement global and regional norms and standards. Strengthen NRAs and regional regulatory mechanisms to progressively reduce the need for prequalification systems.	Encourage countries to apply global norms and standards and adapt them into national/sub-national guidelines and regulations. Build capacity of technical working groups at country level (e.g. NITAG) Invite contributions from countries experts in developing/updating global and regional standards. Strengthen and support NRAs.
Develop evidence-based policy recommendations and guidance.	Develop policy recommendations and support countries to achieve global goals. Develop and coordinate integrated service delivery strategies. Develop outbreak preparedness and response plans. Adapt policies to reflect changes in the health/ immunization environment (e.g., demographic shifts in migration, aging populations, etc.) Develop behavioural strategies to address hesitancy and demand.	Develop, adapt, and apply policies and strategies to the regional context. Communicate with countries about policy recommendations in a timely and efficient manner. Provide technical advice to countries involved in regional policy initiatives.	Encourage countries to adopt regional and global policies and strategies. Strengthen and support NITAGs. Solicit feedback from national technical experts on global and regional policies. Advocate for immunizations and provide reference for immunization policies to be included in country cooperation strategies (CCSs).

TABLE 2. WHO CORE ROLES ENVISIONED FOR 2030 IN IMMUNIZATION AND VACCINES, *continued*

	HQ	REGIONAL OFFICE	COUNTRY OFFICE
Monitor and use data for analytics	Promote development and use of innovative data system technologies. Support regional offices in data collection and analytics. Monitor and analyse global immunization data using best available analytics and visualizations to support decision-making.	Monitor regional health trends by aggregating, validating, analysing, disseminating health-related data. Help countries use regional data to evaluate and strengthen immunization services. Work with countries to generate and interpret data, through modelling and prediction. Provide technical support to countries to link laboratory networks with data systems.	Monitor and evaluate national immunization policies and programmes. Look for opportunities for countries to share information both within and outside the country. Help countries collect and use high quality data for action. Facilitate innovation by promoting new ideas and technologies (including ICT) to make data collection and use more effective and efficient. Build capacities of national authorities to build/sustain national health observatories.
Facilitate implementation and synergies	Coordinate support given to fragile countries. Organize decentralized networks of technical experts to support different aspects of immunization (e.g., supply chain, data quality/surveys, surveillance, etc.) Identify opportunities for synergistic approaches to service delivery and develop appropriate strategies. Coordinate emergency surge capacity.	Participate in the development of CCSs. Support country implementation of international commitments and legal instruments. Lead technical collaboration in countries with no WHO presence. Strengthen technical cooperation among countries and among regions. Provide surge capacity during crisis and emergencies. Give countries more responsibility for managing decisions, technical needs, and financial needs. Engage with and coordinate technical immunization partners.	Encourage countries to adopt regional and global policies and strategies. Strengthen and support NITAGs. Solicit feedback from national technical experts on global and regional policies. Advocate for immunizations and provide reference for immunization policies to be included in country cooperation strategies (CCSs).

ANNEX 3

MATRIX OF THE AREAS OF COLLABORATION BETWEEN WHO AND ITS PARTNERS

TABLE 2. MATRIX OF THE AREAS OF COLLABORATION BETWEEN WHO AND ALL PARTNERS

	TECHNICAL SUPPORT TO COUNTRIES in collaboration with WHO	TECHNICAL SUPPORT TO WHO		
		PRODUCE EVIDENCE	HELP DEFINE NORMS AND STANDARDS AND POLICIES	MONITOR & EVALUATE IMMUNIZATION PROGRAMMES
Countries				
MoH		o	o	o o o
Independent Agencies	o o		o o	
Donors				
			o	
Manufacturers				
UN and Global Initiatives				
	o o o		o o	
Technical Partners				
International Technical Agencies	o o o	o o	o o	o o o
Universities and Research Institutions	o	o o o	o o o	
WHO Collaborating Centres	o o o	o	o	o o o
Scientific Societies	o o	o o	o o o	
Individual Consultants	o o o		o	o
CSOs				
International CSOs	o	o	o	o o o
Local CSOs	o o o			o o o

o o o CRITICAL ROLE for the success of the collaboration

o o IMPORTANT ROLE for the success of the collaboration

o MODERATE ROLE for the success of the collaboration

FINANCIAL SUPPORT TO WHO	FINANCIAL SUPPORT TO COUNTRIES	PRIORITIZE RESEARCH ORIENTATION
o o o	o o o	o
	o	o o o
	o	
o		o
		o o
o		
		o o

ANNEX 4 HISTORIC REVIEW OF 40 YEARS OF EXPANDED PROGRAMME ON IMMUNIZATION

EXECUTIVE SUMMARY OF THE DESK REVIEW

In 2015, WHO commissioned a consultant to undertake a desk study of historical trends and milestones in the field of vaccines and immunization, with the aim to explore underlying factors that have contributed to progress in the 40 years of the EPI.

The study identified the following trends from the immunization coverage data:

- Global immunization coverage has improved dramatically of the past 40 years.
- Immunization systems appear to be sufficiently strong to support new vaccines and antigens being added to the EPI programme (at global level), which can result in protection against more diseases.
- The gap in coverage between the first and third dose of a DTP containing vaccine has decreased, possibly indicating that systems have become stronger.
- Equity in immunization coverage has improved and the total number of unimmunised children has decreased.
- Coverage trends differ substantially between regions.

The number of conditions that are preventable by vaccines have increased since 1974 and immunizations now prevent disease, disability and death from cervical cancer, diphtheria, hepatitis B, measles, pertussis, pneumococcal and *Haemophilus influenza* type b infections, polio, rotavirus diarrhoea, rubella and tetanus. Annual benefits from vaccination and global health improvements include around 6 million prevented deaths.

The desk study identified several factors that may have contributed to EPI progress including the standardised vaccination schedule; development and introduction of new antigens and vaccine combinations; greater equity of access between high and low income countries; and progress made towards polio eradication. With newer and additional vaccines the costs have increased but, thanks to partnerships such as Gavi, more expensive vaccines have become accessible to the poorest countries.

Technology developments and innovations relating to the cold chain, EPI management and health systems development efforts appear to have contributed to increased coverage of immunization. Initiatives such as the Universal Childhood Immunization (UCI) and other global and regional

partnerships have further supported immunization improvements. WHO vaccine policy and technical guidance have also been instrumental in supporting the EPI at all levels, most notably WHO position papers and technical guidelines, recommendations from the Strategic Advisory Group of Experts (SAGE) on Immunization and support by technical groups at regional and national levels.

Financial support from the global health community has been crucial to immunization improvements in developing countries. Large investments were made in the 1970s and 80s but in the 1990s, donor funding began to decline. It rose again around 2000 and now includes support from new actors such as philanthropist organizations.

The review found that WHO leadership in the EPI is widely recognised. WHO has a normative role and is seen as the technical expert organization. WHO is further recognised for its work to safeguard vaccine safety and quality and is seen as a convener of partners at all levels.

EXECUTIVE SUMMARY OF INTERVIEWS WITH THOUGHT-LEADERS

In parallel with the desk review described above, WHO also commissioned a consultant to interview ten key informants selected by WHO as leaders or influencers in immunization. The interviews were conducted along a semi-structured question guide during March and April 2015.

In general, the informants perceived that the EPI programme was particularly successful from the late 1970s to the early 1990s. The 1990s was largely seen as a decade when donors and the health community lost interest in immunization with subsequent challenges in funding. This changed at the turn of the millennium when partners came together to create Gavi, the Vaccine Alliance and new actors entered the scene. The past decade has witnessed a positive development with substantially increased funding and several new vaccines becoming available to help countries combat their disease burden.

Key milestones identified by a majority of the informants include: the Universal Childhood Immunization (UCI), where a time-limited target of 80% immunization coverage by 1990 proved a powerful tool to focus attention and resources; cold chain innovation including the cold box and gas/kerosene fridges; the standardized immunization schedule; training and capacity building, including the development of useful approaches, tools and guidelines such as supportive supervision, technical information sheets, coverage surveys, national programme reviews, planning tools and efforts to improve data quality.

While informants agreed about the trends and milestones, views differed substantially regarding the positive or negative effects on EPI of initiatives to eliminate or eradicate disease, most notably polio.

All informants recognised WHO's unique and instrumental role in the EPI and that without WHO, the world would not be where it is today in immunization. Informants suggested that the environment has changed since 1974, with many more actors and more funding becoming available for immunization. Informants viewed this as a positive development while recognising that this new landscape may present both opportunities and challenges for WHO. Informants were rather unanimous in their recommendation for WHO to focus on its current mandate, to be the recognised technical expert organization, to develop norms and standards (the Strategic Advisory Group of Experts (SAGE) on Immunization was particularly noted), and to use its country, regional and international structures, including the World Health Assembly (WHA), to support and convene partners, including new ones. Informants underlined that WHO must work with utmost integrity and some suggested that WHO may have improve the way it communicates about its past and present achievements.

With regards to the future of the EPI, one informant suggested that there is a need for a fundamental transformation from a vaccine delivery platform focusing on immunization coverage to a programme focusing on disease control.

ANNEX 5

SUMMARY OF FINDINGS FROM THE EXPECTATIONS SURVEY

WHAT DO PARTNERS EXPECT FROM WHO IN IMMUNIZATION?

Results from the expectations survey: summary

OVERVIEW

In January 2015 WHO launched a survey to understand what partners expect from WHO in immunization. The survey targeted global, regional and country level colleagues who work with WHO across all areas of vaccines and immunization—from vaccine development and prequalification, to new vaccine introduction, outbreak response and routine immunization.

In total, 35 persons responded to the survey, 56% from global level, 34% from country level and 10% from regional level. The survey was response rate was approximately 39%, which is in line with standard online survey response rates of 24 to 40%. The respondents represented non-governmental organizations (36%), other UN agencies (32%), NITAG members (13%), donors (10%) and government (9%).

The 13 open-ended questions asked for input on areas that WHO does well and what could it improve on at each level of the organization. The questions also asked respondents for their input on the major challenges that hamper WHO's performance in immunization, the areas where WHO should focus its efforts and areas of work that could be done equally well by other partners. Finally, the survey asked for input on what innovative areas of work WHO should be exploring over the coming years.

SUMMARY OF KEY FINDINGS

Across the board, there was consensus that WHO's key role in immunization is to develop policies. Respondents also listed surveillance, data collection, prequalification of vaccines and equipment, and global coordination as core WHO roles.

Results were more mixed on technical support and research. While some participants felt these were areas WHO should lead, others felt that technical support, research, communications and cold chain were areas could be addressed equally well by other organizations. Respondents felt that WHO's performance in immunization is hampered by bureaucracy and a lack of focus, along with being too reliant on donor funding. In addition, WHO's personnel were seen as, in general, not being up to the task.

When asked what changes they would implement if they were in charge of immunization at WHO, respondents said they would improve coordination and collaboration with partners, improve relationships across all levels of the organization, ensure appropriate staffing and skills amongst staff, and integrate immunization activities (i.e., measles-rubella elimination, polio eradication, and routine immunization). Although less commonly than those areas mentioned above, respondents also said they would address the need for clear routine immunization guidance, strengthen surveillance, focus on resource mobilization at country level, implement the eradication strategies and change the way regions/country offices work to focus on concrete deliverables, rather than outputs.

The survey also asked respondents to identify the most innovative immunization related activity that WHO could undertake in the next 10 years. Responses highlighted the use of information technologies for impact (i.e., to improve data quality, to monitor immunization performance via SMS, to establish an electronic registry), vaccines and delivery system innovation (i.e., innovative vaccine storage and delivery strategies, more thermostable vaccines, simplified cold chain) and improving WHO itself (i.e., eradicating bad management, aligning behind one topic, and transitioning tasks to regional and country office, and eventually to ministries of health).

Global level feedback

» At global level, respondents felt WHO did well at: setting policies and developing guidance, pre-qualification, SAGE, as well as convening experts and partners. They felt WHO/HQ needed to work on: coordination and coverage/ data quality, developing more operational guidelines and ensuring better access to WHO information and policies.

Regional level feedback

» At regional level, respondents felt WHO did well at: providing technical assistance, convening, EPI manager meetings, training, setting regional technical recommendations and managing relationships with ministries of health. They felt WHO/regional offices could improve on: coordination, being more open to working with partners, being more 'country focused' (i.e., providing more direct support to countries), being more innovative, and strengthening outbreak response and surveillance.

Country level feedback

» At country level, respondents felt WHO did well at: providing technical assistance and working with the ministries of health, supporting NITAGs/ Inter-Agency Coordination Committees and coordinating partners. They felt WHO/country offices could improve on: surveillance, coordination and collaboration, holding governments accountable, quality and timeliness of data, having the right human resources capacity and stronger capacity for outbreak response.

WHO Microarray Patch (MAP) Product Development Workshop

Geneva, Switzerland, 8 December 2015

Executive Summary

Background and objectives of the workshop

In line with the Global Vaccine Action Plan (GVAP), WHO's mission is to increase equitable vaccine coverage against vaccine preventable diseases, as well as to accelerate development, approval and implementation of new vaccines and delivery technologies. Microarray patches (MAPs) are a novel vaccine delivery methodology that has the potential to become a game-changer (otherwise known as a disruptive technology) for immunization programs in low- and middle- income countries (LMICs), which mostly rely on vaccine storage and transportation at 2-8°C and trained healthcare workers to administer injectable vaccines by needle and syringe.

MAPs are currently in preclinical development for a number of existing vaccines, including influenza, tetanus toxoid, measles-rubella, inactivated poliomyelitis vaccine (IPV), as well as for vaccines in development such as inactivated rotavirus and dengue. However, there are a number of unknowns with respect to the appropriate product development strategy and the most expeditious regulatory pathway to licensure, since this is considered a novel vaccine combination product. In addition, the desired product characteristics and perceived impact for a particular vaccine/MAP combination in LMIC and high income country (HIC) markets may differ, resulting in a complex and potentially weak value proposition for vaccine and MAP developers to invest in this innovative technology. This workshop sought to better define and tackle the technical, economic and programmatic challenges facing vaccine/MAP product development, to establish assumptions or scientifically-based evidence where they are known, and to propose areas of focus and research where it is needed.

The WHO Department for Immunization, Vaccines and Biologics convened patch developers, vaccine manufacturers, regulators, funders and other key stakeholders to discuss these issues. This high level summary captures the major conclusions and recommendations; a more detailed paper on the considerations for MAP product development will be forthcoming.

Vaccines that may be applicable to MAP delivery

PATH has developed a broad framework to evaluate the potential benefits of new vaccine improvement and/or delivery technologies that, if available and implemented, could significantly impact vaccine accessibility and improve coverage. MAPs have emerged from this analysis as offering clear advantages for vaccine delivery, including increased vaccine thermo-stability, reduced packaging volume, ease of delivery, safer administration and disposal—possibly enabling delivery in new scenarios such as by minimally trained health workers and volunteers. Such attributes would significantly ease the logistics and reduce cost of vaccine delivery, which would be particularly impactful for increasing the coverage and equitable use of vaccines that are highly effective, but challenging to deliver. MAPs may also offer an attractive platform for vaccines targeted to HIC markets or outbreak scenarios, where they could conceivably be delivered to intended recipients with minimal supervision.

The 'most appropriate' vaccine with which to establish immunological and regulatory precedent for the MAP technology, whilst also representing a reasonable investment case, was discussed throughout the meeting. Currently three patch developers have been engaged by the Global Polio Eradication Initiative at WHO and BMGF to develop MAPs for delivery of IPV and are currently in preclinical and manufacturing process development with Phase I/IIa studies anticipated to start in late 2016 or early 2017. From a public health perspective, IPV/MAP may facilitate maintenance of

the high coverage rates as the oral poliomyelitis vaccine (OPV) is being phased out, and be amenable to efficient stockpiling for outbreak responses. However, the development pathway beyond Phase I is yet to be defined, and the partnership or commercialisation plan needs still to be developed with stakeholders.

Patch developers are also assessing delivery of influenza vaccine, for which it is possible to demonstrate rapid clinical proof of concept (POC) using hemagglutination inhibition titre as a correlate of protection. Stability of influenza vaccine at elevated temperatures appears to be feasible and early clinical data is encouraging with the demonstration that seroconversion rates and absolute antibody titers at 1 mo post immunization (full dose) are similar or superior to i.m. administration, which suggests the possibility of dose sparing. Seasonal influenza appears to offer a more compelling MAP business case for vaccine manufacturers, however commitment to development beyond phase I, which will include process scale up and investment in manufacturing infrastructure, is not clear.

Delivery of measles/rubella (MR) vaccine by MAP would confront a clear and urgent public health need. There are approximately 140,000 deaths per year due to measles and a further 110,000 cases of congenital rubella syndrome despite the availability of a safe, effective and affordable vaccine. The reasons for the immunization gap are several, including stringent cold chain requirements, reluctance to 'waste' vaccine by opening a large multi-dose vial and the need for careful reconstitution, handling and sharps disposal. For these reasons, routine immunization coverage remains sub-optimal and house-to-house campaigns to deliver these vaccines by needle and syringe are not feasible, and an alternative methodology, such as MAP, is desperately needed to reach the last mile.

The value proposition of MAP delivery of Measles and Rubella (MR) Vaccine

Although MR/MAP is a clear public health priority, HIC markets would seek vaccines that also contain mumps and potentially varicella (MMR/V). Accessibility to the HIC market segment may incentivise investment, however the technical feasibility of mumps or varicella vaccine delivery by MAP is not known, the inclusion of these components will increase the cost, and the likely development pathway and timeline for a quadrivalent vaccine on a novel delivery platform is likely to be protracted and complex. From the WHO perspective, the need for an alternative vaccine delivery strategy for MR is the most urgent need if we are to close the immunization gaps in LMICs, so that elimination and ultimately eradication of measles and rubella may become achievable in the nearer term.

As with any innovation, there are a number of key assumptions which support the notion that the new product will ultimately be cheaper and/or better. In the case of MR/MAP, the hypotheses are that: efficacy, safety and the total systems effectiveness will be comparable to if not better than MR delivery by syringe and needle; that end-users and vaccine recipients will prefer MAPs to injections; that MAP performance will be consistent across geographical populations, ages and vaccinator skill level, and that there is a feasible regulatory pathway to approval and implementation. At this stage in development, a number of these aspects are unknown, or not yet described. In addition, the demand forecast for MR/MAPs is not clear; current estimates are that 150 million doses of MR are required annually for campaign use, and up to 2 x 134 million doses (based on the birth cohort) for routine use, but a model defining the transition and scale up to a MAP based vaccine, and the use of this product in routine immunization would inform the potential return on investment.

In order to define the acceptability and suitability of a MR/MAP product, the Vaccine Packaging and Product Advisory Group (VPPAG) and the Delivery Technologies Working Group are currently engaging in a consultative process to develop a draft Preferred Product Characteristics (PPC) document to guide both MAP developers and vaccine manufacturers, as well as global stakeholders.

The PPC can inform vaccine impact modelling studies, and sensitivity analyses will help to better understand the trade-offs and tolerances between the various product attributes.

Preferred product Characteristics (PPC) for an MR/MAP product

The MR/MAP PPC seeks to define the acceptable and optimal attributes, specifically for use in LMIC settings. In this context, the appropriate ranges may differ from industry derived target product profiles (TPPs) that are commercially focused. WHO PPCs are nonetheless critical as they describe the attributes that would meet the requirements for WHO prequalification, which is a pre-requisite to vaccine procurement by UN Organizations (e.g. UNICEF, PAHO Revolving Fund) and implementation in GAVI eligible countries.

Since MR/MAP is considered a novel[1] vaccine combination product, the features that define the desired attributes need to be established. The following are some characteristics that were identified as needing further consideration:

- Requirement for thermo-stability: Stabilization of a vaccine up to 40°C to enable transportation and storage out of the cold chain or in controlled temperature chain (CTC) is ideal, however the absolute requirement for this will depend on other factors that may impact programmatic cost and logistical complexity, such as packaging volume or waste disposal;
- The use of an applicator: whilst a MAP that does not require an applicator would be preferable, one may be needed, and there are relative merits of a single use compared to multi-use applicator (cost vs validation requirements regarding contamination and performance reproducibility);
- The wear time: shorter contact time is preferable, particularly if wear time must be supervised. Duration and ease of administration of the MAP is critical to programmatic feasibility and human factor studies will have to evaluate this.

Manufacturing considerations

There has been much debate regarding the need for aseptic manufacturing of MAPs considering that the patches are exposed to a non-sterile environment upon administration, applied to non-sterile skin, and do not deliver vaccine parenterally. To date, early stage clinical studies with both vaccine and small molecules have been performed with 'low-bioburden' clinical material in which general safety and endotoxin levels of the MAPs are acceptable. In cases where a licensed vaccine has been administered by MAP, a repeat dose (and reproductive) toxicology study may not be necessary. However this will be subject of further consultations with the relevant regulatory authorities from countries where clinical trials are planned to be conducted and countries that use the vaccine.

With this in mind, a development strategy in which clinical POC studies are performed with non-aseptic MAPs, and in which the aseptic manufacturing process is scaled up in parallel to phase II POC studies to produce the three consistency batches in readiness for phase III testing, would shorten the timeline to clinical POC data whilst reducing the capital investment at risk. However this proposed strategy will require in depth consultation with the competent regulatory authorities based on the supportive data from the manufacturing process. Whether non-aseptic manufacturing would be acceptable for commercial product remains a question and would be dependent on the generation of supporting data for regulatory review as well as the risk tolerance of the manufacturer.

[1] With "novel" a new innovative vaccine is meant, in contrast with a "new" vaccine, which can be an old technique produced by a new manufacturer. Regulatory requirements are more severe for a novel compared to a new vaccine.

Currently, MAPs can be produced on a small scale (up to hundreds) in a GMP-like environment. Investment into the construction of a pilot plant that is able to aseptically produce several hundred thousand MAPs annually will be needed to support phase III studies and initial commercialisation. Currently this is a significant gap in the development strategy for MAP delivery of any vaccine, and capital expenditure estimates vary significantly. Full costs for manufacturing scale-up, clinical, and regulatory development may require investment of tens to hundreds of millions of dollars. The willingness to invest in such infrastructure will likely only emerge following technical feasibility including clinical POC for a target vaccine, and an understanding of the demand and business case for a particular vaccine/MAP combination. The platform potential of MAPs could also support the value proposition, i.e. how much knowledge from the development of vaccine/MAPs for one indication can be transferred to another. Even once facility plans are in place, the timeframe from breaking ground to a fully validated operational pilot plant is 2-3 years. This will significantly delay the timeline to commercialisation if the investment in manufacturing infrastructure is deferred until clinical POC data are available, particularly if investment is dependent on a platform based approach requiring data from multiple vaccines.

Regulatory pathways

It is assumed that the Biological Licensing Application (BLA) or Marketing Authorization Application (MAA) for the vaccine/MAP product will be submitted by the vaccine manufacturer who already holds a license to manufacture and commercialise the vaccine. The optimal regulatory pathway will depend somewhat on whether the vaccine/MAP product is intended for use in LMICs only, or will also be marketed in HICs.

For a vaccine that is targeted solely for use in LMIC countries, such as MR, the most accelerated route for this target market is through the European Union's (EU), EMA Article 58 Regulation pathway, as this ensures early engagement of WHO prequalification (PQ) and facilitation of in-country vaccine registration and procurement mechanisms. Article 58 allows the Agency's Committee for Medicinal Products for Human Use (CHMP) to issue a scientific opinion, in co-operation with the WHO. WHO PQ would ensure the quality, safety and efficacy of the vaccine/MAP, and that prequalified products are clinically and programmatically suitable for the intended target population and use in national immunization programmes. WHO PQ is reliant on licensure/registration by the responsible NRA in which the vaccine/MAP is manufactured, and WHO can support user country NRAs in LMICs for oversight and registration of PQ'd vaccines.

The product could also be licensed directly in countries of use through their national licensure procedure.

If other markets are also targeted, EMA's Article 58 pathway might not be the ideal route. Depending on the chosen strategy[2], an Article 58 review could be initiated followed by a EU license provided that at that time point the applicant has submitted a Paediatric Investigation Plan (PIP) approved by the EMA's Paediatric Committee. In this case, the vaccine manufacturer must seek approval by the 'competent' supervising regulatory authority of the country of manufacture, such as the FDA or EMA (for products produced in these countries).

In the case of influenza, the MAP presentation would be considered a novel vaccine product that does not have appropriate comparators already authorised or used, and in this case demonstration of efficacy against relevant clinical outcomes in appropriate populations would likely be required to

[2] One could envisage going first for a positive opinion for use outside the EU with a fast PQ, followed by a license in the EU, based on public health arguments and greater needs of the product outside the EU.

support an authorisation in the EU. It may be possible to demonstrate efficacy in some age and population sub-groups and extrapolate to others based on immune response data.

The MAP presentation is considered as an interesting and innovative development and thus developers are strongly recommended to discuss their development plans with national regulatory authorities even during the very early stages of clinical development.

Summary and next steps

This meeting served to increase understanding of vaccine MAP delivery technology, particularly with regulators, donors, WHO and some vaccine manufacturers for whom this has not been a focus to date. Regular (annual) meetings that convene device developers, vaccine manufacturers and others to focus on regulatory requirements and development strategy would be extremely beneficial to review progress, and discuss needs and next steps. Working with its partners, and resources permitting, WHO would continue to support MR/MAP development by focusing on the following activities going forward:

- Through the VPPAG Delivery Technology WG consultation process, finalise the first version of the MR/MAP PPC to help guide developers and manufacturers
- Develop the strategic demand forecast and implementation strategy for MR vaccine on MAP to inform investment decision making
- An assessment on how house to house vaccination would impact easier administration and increase vaccination coverage of MR vaccine, over and above fixed post campaigning
- Convene a focus group of regulators and policy makers to define the regulatory pathway (roadmap) and data requirements for approval and implementation of MR vaccine on MAP.

Although specific to MR, these efforts would benefit MAP development for other vaccines, such as IPV, by setting precedence with regard to process, but also informing some of the translational product development elements, such as production and characterisation data requirements.

Essential medicines and health products

Public consultation on ideas for potential platforms to support development and production of health technologies for priority infectious diseases with epidemic potential (as posted on the web at http://www.who.int/medicines/ebola-treatment/public_consult_platform-tech/en/, accessed March 2016

The R&D Blueprint for infectious diseases with epidemic potential

An efficient and effective research response during an infectious disease epidemic requires preparedness – work done between epidemics to fill knowledge gaps, identify potentially useful candidate medical products and other interventions, and to ensure the timely availability of such when the next epidemic occurs. Following a request from its Member States, the World Health Organization (WHO) is pioneering a global effort, through the R&D Blueprint, to increase R&D preparedness for future epidemics. The Blueprint will promote research to better understand the human-pathogen interface and to generate safety data from Phase 1 studies in man for the most promising experimental products for priority infectious diseases before the outset of an outbreak. It will also facilitate an enabling environment to conduct R&D during an emergency. This public consultation on ideas for platforms to develop and produce relevant health technologies is one activity within the Blueprint.

Executive Summary

The epidemic of Ebola Virus Disease (EVD) in West Africa showed that the world is unable to develop effective interventions in a timely manner for control of severe emerging infectious diseases using current R&D approaches to vaccine, drug and diagnostics development.

The WHO is soliciting ideas for platform technology solutions that are sufficiently flexible to develop and manufacture candidate products for clinical trials in a timely manner (months rather than years) against a variety of infectious disease threats. Such production platforms should focus on a prioritized list of 5 to 10 severe emerging diseases with the potential to generate a public health emergency.

Proposals should include plans for scaling up candidate products at an appropriate scale to contribute to epidemic control, if and when needed. Products resulting from this process should be available and affordable for public health use in low and middle income countries (LMICs). Proposals should explain what internal resources will be used and what external funding will be required to implement the platform concepts being proposed. Creative approaches are encouraged to develop options that include meaningful participation by entities in LMICs. Options that will result in a strategic geographic distribution of platform production sites, in countries with oversight by a WHO-recognized National Regulatory Authority, are especially welcomed.

Proposals received will be evaluated in a first round by a panel of experts convened by the World Health Organization (WHO). Proposers of the best Round 1 proposals will be invited to submit a more detailed plan as part of a Round 2 evaluation step.

While WHO does not intend to provide direct financial support to any proposal, the most meritorious plans emerging for Round 2 evaluation will be presented for consideration to WHO Member States and other organizations which fund Research and Development, in order to seek financial support for establishment of the platforms.

Background

Current, market-driven models of medical R&D do not cater for the application of medical technologies for diseases that are sporadic or unpredictable, especially when they occur in countries with low investment in health infrastructure and delivery. The challenge becomes even greater when faced with a wholly new disease such as SARS, MERS and Nipah virus infection, which are just three examples of diseases that have emerged at the human-animal interface in the last two decades.

The international community needs to invest to improve our ability to respond to new threats and to prepare itself with a novel R&D paradigm to address future epidemics.

Objectives

The World Health Organization (WHO) is inviting ideas on how to improve research and development readiness against priority infectious disease threats. Specifically, proposals are requested for flexible development and production platform technologies to manufacture candidate products for evaluation in Phase 1 clinical trials before any confirmed epidemic threat, as well as for Phase 2 and 3 clinical evaluations during a potential epidemic. The scope of health products which will be considered includes vaccines, therapeutics (drugs and blood products), and diagnostics against 5 to 10 top priority diseases, to be defined by WHO.

Candidate products developed through this mechanism and that are found to have a favourable benefit-risk profile should be available in sufficient quantity to enable potential use in disease control efforts. Therefore the proposals should go beyond preparing materials for Phase 1 clinical studies only and include strategies to assure readiness for production at an appropriate scale to contribute to epidemic control.

Candidate products developed through this process should be affordable for use in populations in which they are tested and/or needed. The priority pathogens may affect any country but options to address affordability in low and middle income countries (LMICs) need to be included in each proposal.

The manufacturing process must be capable of meeting WHO norms and standards, where they exist, and WHO-requirements for emergency listing of a product or, where appropriate, prequalification. Proposals that will result in a strategic geographic distribution of platform production sites, in countries with oversight by a WHO-recognized National Regulatory Authority, are especially welcomed.

Proposals received will be evaluated in a first round by a panel of experts convened by the World Health Organization (WHO). Successful Round 1 applicants will be invited to work with WHO to develop in Round 2 an operational and costed plan, with agreed milestones. WHO reserves the right to suggest the grouping of complementary proposals into a larger collaborative project. Round 2 plans will likewise be evaluated by a panel of experts, and the best proposals will be presented to potential funders for their consideration.

Requirements

Only proposals that can address more than three priority pathogens will be considered. Products developed through the platform technologies will need to comply with target product profiles, or at least clearly be compatible with developing country needs, and to obtain regulatory approval before use in research studies, and thus proposals utilizing technologies that are known to regulatory authorities will be prioritized. Completely novel platform technologies are not excluded but will require inclusion of a realistic regulatory plan. Furthermore, products developed through the platform technologies must be capable of meeting, in due course, WHO prequalification requirements.

Award

This public consultation on ideas will not result in funds being awarded. Rather, it will enable a selection of appropriate proposals to be presented to potential funders for decision-making. Proposers are expected to include a justified budget needed to operationalize the plans contained in the proposal. The proposals should also explain what internal resources will be used and what external funding will be required to implement the platform concepts being proposed.

Collaborations

A key goal of this consultation is to encourage the development of options that include meaningful participation by entities in LMICs. The strength of the collaborations included in the application will be one of the evaluation parameters. The scope of the collaborations is not pre-specified by WHO, and we welcome creative ideas. WHO reserves the right to suggest additional collaborations, based on our knowledge of potential partners for the proposed work. Any such additional collaborations would be subject to agreement by the original proposers.

Application process

A. **Key dates**

a. Submission of applications by Friday 5 February 2016, 1700 Geneva time
b. Workshop to present the ideas, by 4/6 April 2016
c. Notification of invitation to submit a phase 2 proposal by 25 April 2016
d. Phase 2 proposal deadline (invited proposals only) by Friday 27 May 2016, 1700 Geneva time
e. Selections completed and notifications sent by end of June 2016

B. **Eligibility**

The public consultation on ideas is open to non-profit organizations, for-profit companies, international organizations, government agencies and academic institutions.

C. **How to apply**

Proposals should be submitted electronically to the following email addresses:woodd@who.int with a copy to gracet@who.int

D. **Format**

The proposal should clearly communicate the platform being proposed in not more than 5 pages. The proposal should cover the following elements:

1. **Concepts and ideas:** Describe and justify the rationale for the proposal and the impact the idea will have on R&D readiness.
2. **Proposed technical approach:** Succinctly describe the technical details of the technology platform, including any prior use or experience with other products, and scientific and technical justifications why the platform would be useful for products to address the priority pathogens. It will also be necessary to describe how the technology lends itself to rapid scaling up on demand at the time of an outbreak.
3. **Proposed collaborative approach:** Succinctly describe how meaningful participation by entities in LMICs will be achieved, and the intended strategic geographic distribution of platform production sites. Include a description of the how collaborations between partners will be structured and managed.
4. **Costs and timelines:** Include estimates of costs, per year, of the proposal. Indicate what resources the proposers will donate to the project and, with justifications, what external resources are requested. Indicate what deliverables, in terms of candidate products for the priority pathogens, will become available and over what timelines. Also indicate how affordability of products for LMICs developed through this proposal will be addressed.

Evaluation and selection process

The application review process will be as follows:

1. An initial screening of applications by the WHO secretariat to determine if they are within scope of the request for ideas. Proposals that are out-of-scope will be removed from further consideration, and the applicant informed.
2. Reviews of proposals that are within scope will be conducted by an ad hoc Advisory Group convened by WHO specifically to provide advice on the proposals. This review will be preceded by a workshop at which the responses to the public consultation will be presented with participation from all stakeholders.
3. Experts selected for the ad hoc group will undergo WHO declaration of interest review to identify and manage conflicts of interest. This group will advise WHO on the strengths and weaknesses of the proposals to improve R&D readiness for the priority pathogens. The review will also address the likelihood of meaningful participation by entities in LMICs, and the strengths of the proposed organizational and management structures.
4. Decisions on the proposals that will be invited to submit detailed plans for round 2 will be made by WHO. Additional instructions will be provided at that time. Proposals selected to go forward to round 2 may be subject to suggested modifications.
5. Evaluation of the round 2 proposals will be made by the ad hoc Advisory Group, who will identify proposals that merit consideration for funding support
6. WHO will conduct due diligence reviews of the selected proposals, and propose the platforms for consideration by potential funders.

Contacts

Technical and administrative questions about this Public Consultation should be directed to Dr David Wood (woodd@who.int) with a copy to Theo Grace(gracet@who.int)

Global access and intellectual property

Management of intellectual property (IP) rights is likely to play an important role for the viability of the platform(s). The proposals should explain how IP issues will be managed to ensure fair and equitable access, especially for LMICs, to any product(s) developed through the proposed platform(s).

DECLARATION ON

"Universal Access to Immunization as a Cornerstone for Health and Development in Africa"

Available at: http://immunizationinafrica2016.org/ministerial-declaration-english/, accessed March 2016

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

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

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

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

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

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

Recalling the Heads of State Declaration on Polio Eradication in Africa: "Our Historic Legacy to Future Generations" (Johannesburg, June 2015); the World Health Assembly resolution (WHA68.6) on the Global Vaccine Action Plan (Geneva, May 2015), the commitment made by African Ministers of Health on Universal Health Coverage in Africa (Luanda, April 2014); the Immunize Africa 2020 Declaration (Abuja, May 2014) endorsed by African Heads of State; the World Health Assembly resolution that commits all 194 Member States to apply the vision and strategies of the Global Vaccine Action Plan (GVAP) (Geneva, May 2012), and the African Heads of State endorsement of the Pharmaceutical

Manufacturing Plan in 2012 as the framework for African people to have access to essential, quality, safe and effective medical products and technologies.

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

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

We hereby collectively and individually commit ourselves to:

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

We call upon:

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

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

Done at Addis Ababa on 25 February 2016

Twenty-Ninth Intercountry Meeting of National Managers of The Expanded Programme on Immunization
and
Sixteenth Intercountry Meeting on Measles/Rubella Control and Elimination

Amman, Jordan, 29 November – 3 December 2015

Summary report

The Vaccine Preventable Diseases and Immunization (VPI) unit of the Communicable Disease Prevention and Control Department (DCD) of World Health Organization (WHO) Regional Office of the Eastern Mediterranean (EMRO) organized the Twenty-Ninth Intercountry Meeting of National Managers of The Expanded Programme on Immunization and the Sixteenth Intercountry Meeting on Measles/Rubella Control and Elimination, that were held in Amman, Jordan in the period of 29 November to 3 December 2015.

The objectives of the meeting were to: review countries' progress towards achieving the regional immunization targets, including, routine immunization, measles elimination and hepatitis B control targets; review countries' progress in implementation of the national plans and update the national plans for strengthening routine immunization, measles/rubella elimination and control and hepatitis B control programme; and review the situation of IPV introduction in routine immunization in EMR countries and the situation of preparation for switching from tOPV to bOPV in 2016 and update the related national plans.

The meeting was attended by delegates from 21 countries of the EMR (all except Djibouti), Members of the Immunization Regional Technical Advisory Group (RTAG) and National Technical Advisory Groups (NITAGs), WHO (EPI and POL related staff from country, regional and HQ levels), as well as representatives from different partners including; UNICEF (HQ, Supply Division, ESARO and MENARO and UNICEF country offices), Gavi, the Vaccine Alliance, the US Centre for disease control and prevention (CDC), the Bill and Melinda Gates Foundation (BMGF), the Network for Education and Support for Immunization (NESI), Agence De Medicine Preventive (AMP) and the Eastern Mediterranean Public Health Network (EMPHNET).

Dr. Maria Cristina Profili, WHO representative, Amman, Jordan, inaugurated the meeting and delivered a message from Dr Ala Alwan, WHO Regional Director of the Eastern Mediterranean Regional Office. In his message, the RD noted that vaccination is a key tool for prevention of child deaths and referred to the countries' efforts to achieve the regional eradication, elimination and control targets, including. polio eradication, measles elimination, maternal and neonatal tetanus elimination and hepatitis B control and underlined that reaching high routine immunization coverage in all districts, introducing new life-saving vaccines and technologies, and implementing the accelerated disease control strategies are the key pillars for achieving these

targets. He referred also to the major challenges currently facing the region in connection to the geo-political situation in several countries and their impact on vaccine delivery systems and appreciated the efforts and innovative approaches that have been undertaken in order to keep EPI functioning and to overcome the challenges. 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.

Dr Najwa Khuri-Bulos, Chairperson, NITAG, Jordan and Dr Zein Karar, Chairperson, NITAG, Sudan, chaired the meeting

The meeting entailed sessions on global and regional situation of EPI and measles/rubella control and elimination, strengthening routine immunization in low coverage countries, polio eradication initiative and polio end game strategic plan, progress in achieving and sustaining population immunity against measles and rubella, achieving the target of measles/rubella surveillance system performance indicators as well as discussing the Eastern Mediterranean Vaccine Action Plan (EMVAP).

The meeting included two break-out group works dedicated to discuss, in details, country by country situation in achieving required population immunity and its impact on measles/rubella occurrence and looking at situation of measles-rubella surveillance. A third group work was dedicated to discussing enhancing implementation of objective 2 of the polio end game strategic plan, including IPV introduction and switching from tOPV to bOPV in routine immunization. A fourth group work was dedicated to discussing the EMVAP.

The meeting was actively participated by all. Ample time for discussions was provided during each session and during the work groups. Participants from 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. A memory stick that contained the background materials related to the meeting and all pour point presentations submitted during the meeting was distributed to all participants.

Based on the discussions, the recommendations of the meeting were drafted and presented to the participants at the final sessions. Participants actively participated in commenting, modifying and refining the recommendations.

Recommendations

Preamble:

Participants of the meeting appreciated and commended the efforts of the national EPI programmes in countries of the Region and the devotion of the front-line health workers in the countries in crises for reaching the children in the hard-to-reach areas with life-saving vaccines.

Participants of the meeting commended the efforts of several countries in the region for controlling measles outbreaks through implementation of wide-age range SIAs. In addition, participants congratulated Egypt for the successful implementation of the MR SIAs and commended Egypt and UAE for the successful approach in dealing with vaccine hesitancy during those SIAs.

Participants of the meeting recognized the high quality of measles/rubella surveillance and achievement of the main targets of the surveillance system indicators in several countries and the success in implementation of measles/rubella surveillance under the challenging situation in Syria and Yemen.

Participants of the meeting noted the progress in the interruption of wild polio virus transmission in the Middle East and the Horn of Africa and the decrease in polio cases in Afghanistan and Pakistan. Nevertheless, the participants expressed concern about the difficulty and insecurity the polio teams are facing in this phase of the polio endgame. Participants of the meeting noted the progress in IPV introduction and plans for the switch from tOPV to bOPV in April 2016.

Participants of the meeting noted the progress in introduction of the new vaccines in the region and the progress towards achieving the hepatitis B control target. However, the participants noted with concern the growing threat of vaccine hesitancy in countries of the region and that the region is not on track for achieving 4 of the regional immunization goals (high routine immunization, polio eradication, measles elimination and maternal and neonatal tetanus elimination) and that these goals are unlikely to be achieved in 2015.

Participants of the meeting reiterated the importance of accelerating implementation of the relevant recommendations of the previous meetings. In addition, the following is recommended:

I. Strengthening routine immunization

1. Countries that have not achieved the routine immunization coverage target (at least 90% DTP3-containing vaccine coverage at national level and 80% in all districts) should, with supported from WHO and partners, conduct in-depth analysis of district level immunization data to identify unreached populations and develop/update district microplans with innovative approaches tailored to reach un/under-immunized populations, including those in the hard to reach areas to ensure equity in access to immunization.
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. National immunization programmes are to engage with civil society organizations, professional organizations, religious leaders (expanding on the experience of engaging religious leadership in the region in polio eradication), partners, advocates and champions to enhance trust in vaccines and convey

messages on the value of vaccines and the responsibility of individuals, parents and community to ensure that everyone is protected through vaccination.

3. Immunization programmes in all countries should create partnerships and continuously engage with the media, social media and other communication routes to sustain awareness of the public on the benefits of vaccines and vaccination.
4. All countries are encouraged to register all available WHO prequalified vaccines (including bOPV and IPV), in order to ensure availability of alternate sources of vaccine supply in case of shortage of any vaccines used by the national EPI.
5. WHO and UNICEF are requested to work with partners to encourage manufacturers to apply for registration of all WHO prequalified vaccines (as relevant) in all Member States

II. Implementation of vaccination under humanitarian emergencies

1. WHO is to support the countries facing humanitarian emergency to document the successful strategies, innovative approaches and the lessons learnt in delivery of routine vaccines and implementation of SIAs during the humanitarian emergency situations and share the successful experience with the countries facing similar situations.
2. Local partners who can deliver vaccination in the inaccessible conflict areas should be identified and supported by international partners to deliver routine immunization and SIAs through existing coordination mechanisms.
3. International partners should assist, through existing coordination mechanisms, with mapping of areas where immunization services are interrupted, developing necessary plans for implementation of SIAs and resuming immunization service delivery, support resource mobilization and support strengthening the local capacity to deliver immunization services.
4. Implemented schedule for immunization should be harmonized to ensure equitable access to immunization services for all antigens in all areas of the country.
5. Monitoring and evaluation programme should be instituted to ensure the quality of the delivered services.

III. Decreasing vaccine hesitancy and increasing vaccine demand:

1. Immunization programs are encouraged to assess perceptions, barriers and enablers for increasing vaccination coverage among caregivers and care providers and actively monitor vaccine hesitancy and refusal groups. Countries are to assess the best communication approaches to provide vaccines and vaccination-related information.
2. All countries should develop and implement comprehensive communication and social mobilization strategies to increase community awareness about the risks of vaccine-preventable diseases and the benefits of vaccination and to enhance trust in the immunization program and address concerns using both traditional and new social communication platforms.

3. Immunization programs should ensure the availability of an EPI-trained communication officer and conduct specialized education and training of health care workers on communication skills to rapidly address vaccine hesitancy issues with clients and parents.
4. Immunization programme should create close collaboration, coordination and partnership with the private sector, paediatric and other medical societies to counter vaccine hesitancy messages and address vaccine hesitant behaviours within health care workers and the general public. Inclusion of relevant training into academic and clinical curricula of nursing, medical and other health care professional students and incorporation into continuing education curricula should be implemented.
5. EMRO to develop its human resource and technical capacity for dealing with the growing problem of vaccine hesitancy in the region and provide, in collaboration with partners, the necessary technical support for responding to vaccine hesitancy, conduct the related operational research and build the capacity of the health workers.

IV. Polio eradication

1. WHO and partners are to support the members states in field testing polio preparedness and response plan and conduct training on the outbreak response standard operating procedures
2. Middle East and Horn of Africa countries to effectively use polio asset, knowledge and infrastructure in improving routine immunization coverage through promotion and implementation of the EMVAP and contributions in national public health emergencies like cholera or measles outbreak response, mass exodus, etc.
3. All countries to enhance the sensitivity of the surveillance system and immunization coverage of high risk populations particularly the children of internally displaced people, refugees and migrant communities from polio endemic countries

V. Implementation of Objective 2 of polio eradication end game strategic plan:

1. IPV introduction:

a. Egypt, Iraq and Djibouti are to prepare for introduction of IPV, including, as necessary, cold chain capacity assessment and cold chain capacity upgrading, reviewing the registration and reporting system as well as training of the immunization health workers at all levels.
b. WHO is to support the countries to implement fast track registration of IPV vaccine.

2. Preparing for the switch from tOPV to bOPV:

a. WHO is requested to support countries in the implementation of registration of bOPV vaccine according to updated WHO guidelines.
b. All countries should adhere to the dates of the globally coordinated switch period (17 April to 1 May 2016). Remaining countries that have not decided on the switch day should do so and notify WHO, UNICEF, and partners on the switch day soon.

c. Egypt, Iraq, Libya, and Syria are required to develop national plans of action for implementation of the switch in line with the WHO related guidance, and share the national switch plan with WHO, UNICEF, and partners by 15 December 2015.
d. All countries are to regularly follow up on the national preparations for implementation of the switch, using the switch planning dashboard, to ensure timely completion of all switch-related activities including thorough validation and reporting to WHO as per switch guidelines.
e. All member states should ensure they have adequate operational funds and stock of bOPV by the switch date.
f. WHO and partners are requested to provide technical support to the countries in need in order to ensure smooth implementation of the switch by the global target date.
g. WHO to support the countries in implementing training on the interim and post switch guidelines to respond to VDPV2.

VI. Measles/rubella elimination and control:

1. All countries are asked to include a long-term plan for measles elimination in their cMYP and to develop and implement annual work plans accordingly.
2. All countries are encouraged to use the new WHO guidelines to conduct high quality measles/rubella SIAs, including, readiness assessment tools, intra-campaign performance monitoring and post campaign coverage surveys. Countries should develop plans and ensure budget allocation for mop-up activities based on results of the post campaign evaluation and coverage surveys.
3. The participants reaffirms the recommendation of SAGE that infants from 6 months of age receive a dose of measles containing vaccine in the following circumstances:
    a. during a measles outbreak as part of intensified service delivery;
    b. during SIAs in settings where risk of measles among infants remains high (e.g. in endemic countries experiencing regular outbreaks);
    c. for internally displaced populations and refugees, and populations in conflict zones;
    d. for individual children at high risk of contracting measles (e.g. contacts of known measles cases or in settings with increased risk of exposure during outbreaks such as day-care facilities);
    e. for infants travelling to countries experiencing measles outbreaks;
    f. for infants known to be HIV-positive (see 2009 WHO measles vaccine position paper).

Measles containing vaccine (MCV) administered before the age of 9 months should be considered a supplementary dose and recorded on the child's vaccination record as "MCV0". Children who receive a MCV0 dose should then receive subsequent measles-containing vaccines at the recommended ages according to the national schedule.

4. WHO/ EMRO is requested to expedite establishing Regional Verification Commissions for measles/rubella elimination and hepatitis B reduction goals.
5. All countries should establish a national verification committee (NVC) for measles and rubella elimination in line with EMRO guidelines on establishing national measles/rubella verification committees.
6. All countries are to establish suitable CRS surveillance systems and/or CRS disease burden studies. Countries that have not introduced rubella vaccine are to use the data generated for advocacy and decision-making on introduction of rubella vaccine. Countries that have introduced rubella vaccine are to use these data for monitoring progress towards achieving the national rubella/CRS elimination target.
7. WHO and partners are to provide necessary technical support for establishing CRS surveillance or conducting CRS disease burden studies, including analysis of data and using the data for decision making and mobilizing necessary resources for rubella vaccine introduction.
8. All countries are to strengthen measles/rubella case-based laboratory surveillance and reach the recommended surveillance system performance indicators. Countries should ensure proper coordination and collaboration between epidemiology and laboratory surveillance departments and ensure consistent reporting of data to EMRO.
9. Provincial EPI programmes in Pakistan are to share all case-based surveillance data with the Federal EPI cell and Federal EPI cell is to share the comprehensive data with EMRO.
10. Member states are urged to collect representative specimens for genotype analysis from all outbreaks and report all sequencing data to the international database.
11. All member states should conduct in-depth data analysis, provide regular feedback to reporting source, and develop appropriate responses based on the analysis.
12. To avoid overburdening the laboratory during an outbreak, programs are requested to enhance epidemiologic investigation and linking cases epidemiologically with laboratory-confirmed cases following WHO guidelines. Once an outbreak has been confirmed, further testing should be done every three months or when the outbreak appear in new areas.
13. Countries that face difficulties in specimens transportation within the county or outside the country, including cold chain maintenance, are encouraged to use alternative sampling techniques such as dry whole blood on filter paper spots or oral fluid collection device, which can withstand ambient temperature for around a week.
14. WHO to continue providing the necessary support to strengthen and sustain high quality testing, including, providing training opportunities and monitoring laboratory performance including serology and molecular quality assurance.

VII. Eastern Mediterranean Vaccine Action Plan (EMVAP):

1. Countries are to update their multi-year plans in line with the EMVAP and develop annual immunization workplans in line with the multiyear immunization plan.

Update on the Gavi Board meeting 2-3 December 2015

The Alliance set ambitious targets for 2011-15. During the last five years, we have seen unprecedented progress in immunisation with more children reached than ever before and a dramatic acceleration in vaccine introductions. The average coverage in the 73 Gavi countries reached 81% in 2014, the first time it has exceeded 80%. This is an increase of 3 points since 2010 and means nearly 65 million children in Gavi countries are now being reached with three doses of a DTP-containing vaccine. Thirty-two Gavi-eligible countries now have coverage of over 90%, a sign of the growing strength of many immunisation programmes. It also means that the unreached are increasingly concentrated in a set of large and fragile states, with 20 countries accounting for ~90% of under-immunised children.

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Despite progress made, nearly one in five children is not being reached with the most basic vaccines and only a very small proportion receive all 11 vaccines universally recommended for infants by WHO.

Moreover, only 15 countries have achieved the Global Vaccine Action Plan's equity target of ensuring 80% coverage in every sub-national district. Gavi's new strategy for 2016-2020 calls for innovative approaches and robust data to identify and reach the remaining pockets of under-immunised children and support countries in improving coverage and equity.

Against this backdrop, the Gavi Board has decided on the following areas:

Gavi's measles and rubella strategy

The Board approved Gavi's new measles and rubella strategy, providing a single coherent approach on measles and rubella immunisation. The strategy aims primarily at increasing routine immunisation coverage and puts a strong focus on timely and fact-based planning of measles-rubella interventions. Countries will now be required to self-finance the first dose of measles vaccine in their national immunisation programme, and have a long term budgeted plan for measles and rubella activities, to ensure financial and programmatic sustainability. As such, routine immunisation will be complemented, as needed, by higher-quality, better-planned, more targeted and independently monitored campaigns. Gavi's comprehensive support for measles and rubella will provide countries with predictable financing and hopefully, strengthen country ownership.

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

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

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

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

Gavi's 2016-2020 Strategy goal level indicators and targets
The Board approved the remaining strategic goal-level indicators not included among the set already approved by the Board in June 2015.

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

22 JANUARY 2016, 91th YEAR / 22 JANVIER 2016, 91e ANNÉE
No 3, **2016**, **91**, 21–32
http://www.who.int/wer

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Global Advisory Committee on Vaccine Safety, 2–3 December 2015

The Global Advisory Committee on Vaccine Safety (GACVS), an independent expert clinical and scientific advisory body, provides WHO with scientifically rigorous advice on vaccine safety issues of potential global importance.[1] GACVS held its 33rd meeting in Geneva, Switzerland, on 2–3 December 2015.[2] The Committee examined the clinical and population characteristics of cluster immunization anxiety-related reactions and the detection of vaccine safety signals from spontaneous reporting databases. It also reviewed vaccine-specific safety issues concerning RTS,S malaria vaccine, safety of human papillomavirus (HPV) vaccines, pandemic influenza vaccine and narcolepsy, and the safety profile of smallpox vaccines.

Clusters of anxiety-related reactions following immunization

Clusters of anxiety-related reactions following immunization have affected immunization programmes in several countries and drawn the attention of media and the public globally. Understanding such events, their characteristics, and why they may occur will help to better guide public health efforts to prevent and manage them.

The Committee was provided with updated information on the occurrence of such events in the relevant scientific literature

[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: Mayo Clinic, Rochester MN, USA; Centers for Disease Control and Prevention, Atlanta GA, USA; Dalhousie University, Halifax, Nova Scotia, Canada; University of Geneva, Switzerland; Agency for Medicine Safety, Saint-Denis, France; London School of Hygiene and Tropical Medicine, London, UK; Public Health England, London, UK; Uppsala Monitoring Centre, Uppsala, Sweden; Sanofi Pasteur, Lyon, France; and Bavarian Nordic, Kvistgard, Denmark.

Comité consultatif mondial de la sécurité vaccinale, 2 et 3 décembre 2015

Le Comité consultatif mondial de la sécurité vaccinale (GACVS) est un organe consultatif indépendant composé d'experts cliniques et scientifiques qui fournissent à l'OMS des conseils d'une grande rigueur scientifique sur des problèmes de sécurité vaccinale susceptibles d'avoir une portée mondiale.[1] Le GACVS a tenu sa trente troisième réunion à Genève (Suisse) les 2 et 3 décembre 2015.[2] Le Comité a examiné les caractéristiques cliniques et démographiques des grappes de réactions liées à l'anxiété à l'égard de la vaccination et a discuté de la détection des signaux de sécurité vaccinale à partir des bases de notifications spontanées. Il s'est également intéressé à l'innocuité du vaccin antipaludique RTS,S, à la sécurité des vaccins contre le papillomavirus humain (PVH), au risque de narcolepsie associé au vaccin contre la grippe pandémique, et au profil d'innocuité des vaccins antivarioliques.

Grappes de réactions anxieuses postvaccinales

Les programmes de vaccination de plusieurs pays ont été confrontés à des grappes de réactions anxieuses postvaccinales, attirant l'attention des médias et du public dans le monde entier. Il importe de comprendre ces manifestations et d'en cerner les caractéristiques et les causes pour orienter les mesures de santé publique susceptibles de les prévenir, et d'en améliorer la prise en charge.

Le Comité a pris connaissance des informations actualisées concernant la survenue de ces manifestations, tirées de publications

[1] Voir N° 41, 1999, p. 337-338.

[2] Le GACVS a invité d'autres experts à présenter et à analyser les données relatives à des sujets particuliers. Il s'agissait notamment de personnes affiliées aux organismes suivants: Mayo Clinic, Rochester MN (États-Unis d'Amérique); Centers for Disease Control and Prevention, Atlanta GA (États Unis d'Amérique); Université Dalhousie, Halifax, Nouvelle-Écosse (Canada); Université de Genève (Suisse); Agence nationale de sécurité du médicament, Saint-Denis (France); École d'hygiène et de médecine tropicale de Londres (Royaume-Uni); Public Health England, Londres (Royaume-Uni); Centre de pharmacovigilance d'Uppsala (Suède); Sanofi Pasteur, Lyon (France); et Bavarian Nordic, Kvistgard (Danemark).

WORLD HEALTH ORGANIZATION
Geneva

ORGANISATION MONDIALE DE LA SANTÉ
Genève

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

01.2016
ISSN 0049-8114
Printed in Switzerland

and the media and social media reports from several countries including: Iran (tetanus toxoid vaccine 1992); Italy (hepatitis B vaccine 1995); Jordan (diphtheria tetanus vaccine 1998); India (tetanus toxoid vaccine 2001); Viet Nam (oral cholera vaccine 2001); Australia (HPV vaccine 2007); Taiwan, China (H1N1 influenza 2009); and the United States of America (H1N1 influenza 2010). The GACVS observed that these clusters occurred in rural and urban settings both in high and low income countries from all continents and involved different vaccines. Children of both sexes were affected, though with a higher frequency of girls than boys in some studies. Occurrence of reactions was usually within the first 15 minutes of vaccination and involved mostly school-age children. The reactions manifested with a wide variety of symptoms. Most clusters involved introduction of a new vaccine or a change in the routine programme such as new age group or new setting. A small cluster that started in a group setting could spread quickly to form a larger outbreak involving several clusters. Response to such clusters varied in different countries, as did its impact on vaccination programmes. Public health interventions to regain community trust after such events were often costly and resource-intensive.

scientifiques pertinentes, des médias traditionnels et des médias sociaux de différents pays, notamment: l'Iran (vaccin à base d'anatoxine tétanique, 1992); l'Italie (vaccin contre l'hépatite B, 1995); la Jordanie (vaccin antidiphtérique-antitétanique, 1998); l'Inde (vaccin à base d'anatoxine tétanique, 2001); le Viet Nam (vaccin anticholérique oral, 2001); l'Australie (vaccin contre le PVH, 2007); Taïwan, Chine (grippe H1N1, 2009); et les États-Unis d'Amérique (grippe H1N1, 2010). Le GACVS a constaté que ces grappes surviennent tant en milieu rural qu'urbain, à la fois dans les pays à revenu faible ou élevé, sur tous les continents, et avec différents vaccins. Les enfants des 2 sexes sont touchés, avec toutefois une plus grande fréquence chez les filles que chez les garçons selon certaines études. Les réactions, qui apparaissent généralement dans les 15 minutes qui suivent la vaccination, concernent principalement les enfants d'âge scolaire. Elles se manifestent par une grande variété de symptômes. Dans la plupart des grappes, ces réactions sont survenues lors de l'introduction d'un nouveau vaccin ou d'une modification du programme de vaccination systématique, par exemple l'ajout d'une nouvelle tranche d'âge ou d'un nouveau contexte de vaccination. On a constaté qu'une petite grappe apparue au sein d'un groupe donné pouvait se propager rapidement pour donner lieu à une plus grande flambée, mettant en jeu plusieurs grappes. La riposte suscitée par ces grappes et leur impact sur les programmes de vaccination variait d'un pays à l'autre. Les interventions de santé publique menées pour regagner la confiance des communautés après de telles manifestations étaient souvent coûteuses, exigeant des ressources importantes.

A survey carried out in 12 low and middle income countries in October 2015 found that many countries are aware of such events. Fainting events are most commonly reported. The survey also found that short-term consequences included a decrease in public confidence in vaccines, resulting in decreased coverage and concerns and fear among health-care personnel to vaccinate; however, there were no long-term or major impacts on their immunization programmes, mainly due to prompt responses. It was observed that there are gaps in surveillance systems for adverse events following immunization (AEFI) in countries, such that various anxiety-related AEFIs are not well defined and reported or are grouped with other AEFIs, therefore not capturing the true burden.

Une enquête réalisée dans 12 pays à revenu faible ou intermédiaire en octobre 2015 a indiqué que de nombreux pays sont conscients de la survenue de ces manifestations. L'évanouissement était le symptôme le plus souvent signalé. L'enquête a également montré qu'à court terme, ces incidents entraînaient une baisse de confiance du public à l'égard de la vaccination, se traduisant par une diminution de la couverture vaccinale et un sentiment d'inquiétude et de crainte du personnel soignant devant administrer les vaccins; cependant, aucun impact majeur n'a été observé à long terme sur les programmes de vaccination, ce qui est essentiellement dû à la rapidité des interventions. Le Comité a noté qu'en raison des lacunes des systèmes nationaux de surveillance des manifestations postvaccinales indésirables (MAPI), les MAPI liées à l'anxiété sont souvent mal définies, insuffisamment signalées ou regroupées avec d'autres MAPI, la charge réelle de ces manifestations n'étant ainsi pas bien mise en évidence.

The use of terms suggesting psychological disorders for severe anxiety reactions were observed to be problematic for vaccinees because of the stigma and consequences that were related to such labelling. Failure to differentiate between the clinical manifestations of fainting, anxiety and associated hyperventilation and other conditions such as anaphylaxis, resulted in mismanagement of cases and thereby additional avoidable harm.

L'emploi de termes évocateurs de troubles psychologiques pour décrire les réactions anxieuses sévères s'est avéré inopportun pour les personnes vaccinées en raison de la stigmatisation et des conséquences associées à ces termes. La distinction entre les manifestations cliniques d'évanouissement, d'anxiété et d'hyperventilation associée et certaines autres affections comme l'anaphylaxie n'était pas toujours correctement établie, entraînant une prise en charge inadéquate des cas et des préjudices supplémentaires qui auraient pu être évités.

GACVS also reviewed in detail the cluster immunization anxiety reactions that recently occurred on the occasion of a mass measles immunization campaign in a European country. There are increasing reports of occurrence of such reactions with expansion of age of immunization to school children and young adults. Little knowledge and understanding of such events by health

Le GACVS a également examiné en détail la grappe de réactions anxieuses à l'égard de la vaccination qui s'est récemment manifestée lors d'une campagne de vaccination de masse contre la rougeole dans un pays européen. Ces réactions sont signalées en nombre croissant depuis l'extension de l'âge de vaccination aux enfants d'âge scolaire et aux jeunes adultes. Il a par ailleurs été constaté que ces manifestations sont souvent mal comprises

workers was also documented. Fast spreading of rumours, fears and concerns of "unknown events" through media and social networking using modern communication technologies was observed and may have aggravated the situation. These events have high visibility and, if not adequately assessed and managed, can convert from a cluster of immunization anxiety events that can be easily managed onsite into a real medical problem with a detrimental impact on the individual affected and on the immunization programme. It was observed that good pre-campaign preparation, such as creating awareness of such events and training of health staff, engagement of communities and appropriate media and communication strategies were important for prevention of such events.

GACVS acknowledged that the magnitude of the impact of immunization anxiety reactions is not currently recognized in the medical literature. Several gaps have been identified including the need for case definitions that span the different degrees of anxiety reactions and for guidance on how to recognize, manage and prevent immunization anxiety reactions. It is also important to identify communication strategies tailored to the audience and plan interventions for first responders, hospitals and immunization programmes in order to improve recognition and management of immunization anxiety clusters, and limit their continuation and spread. There is need to conduct research on predisposing factors for such clusters, outbreaks and the role of social media. Other key areas that need to be addressed include defining effective practices for prevention and intervention in different settings. It was also noted that such clusters need not be immunization-specific and may occur in several other contexts. Finally, GACVS also noted that lack of recognition, lack of early onsite intervention, excessive hospitalization and overreaction by healthcare providers and programme managers to such episodes have the potential to aggravate the problem.

Vaccine safety signals from the Uppsala Monitoring Centre database

As requested by GACVS in June 2015, the Secretariat presented 3 recent vaccine safety signals documented by the Uppsala Monitoring Centre (UMC) in April and July 2015. These signals were associated with HPV vaccines and gastrointestinal motility disorders, rabies vaccines and erythema multiforme, and bullous pemphigoid in infancy after vaccination. Based on this experience, the GACVS discussed a process for the review of vaccine safety signals transmitted by UMC and criteria for further action by the Committee.

The UMC has developed a worldwide database of spontaneous individual case safety reports (ICSR) concerning health products, named Vigibase, under the WHO Programme for International Drug Monitoring. Within Vigibase, UMC applies a Bayesian algorithm on the

et méconnues des agents de santé. Des rumeurs, des peurs et des inquiétudes au sujet de «manifestations inconnues» se sont rapidement propagées dans les médias et les réseaux sociaux à l'aide des technologies modernes de communication, ayant probablement aggravé la situation. Du fait de leur grande visibilité, ces manifestations d'anxiété liées à la vaccination peuvent prendre de l'ampleur si elles ne sont pas correctement évaluées et prises en charge, passant d'une grappe aisément gérable à un véritable problème médical avec des conséquences dommageables sur les personnes atteintes et les programmes de vaccination. On a observé qu'il est important, pour prévenir ces incidents, de faire un travail de préparation adéquat avant les campagnes de vaccination, consistant notamment à sensibiliser et à former les agents de santé à ces manifestations, à établir un dialogue avec les communautés et à élaborer des stratégies médiatiques et de communication appropriées.

Le GACVS a constaté que l'ampleur de l'impact des réactions anxieuses postvaccinales n'est actuellement pas reconnue dans la littérature médicale. Plusieurs lacunes ont été identifiées. Il faudrait notamment des définitions de cas couvrant différents degrés de réactions anxieuses, ainsi que des orientations sur la manière de reconnaître, de prendre en charge et de prévenir les réactions anxieuses à l'égard de la vaccination. Il importe également d'identifier les stratégies de communication les mieux adaptées au public visé et de prévoir des interventions auprès des secouristes, des hôpitaux et des programmes de vaccination pour améliorer la reconnaissance et la prise en charge des grappes de réactions anxieuses postvaccinales et limiter leur durée et leur propagation. Des travaux de recherche devraient être menés sur les facteurs de prédisposition favorisant la survenue de ces grappes, sur les flambées et sur le rôle des médias sociaux. Il est en outre essentiel de définir des pratiques efficaces de prévention et d'intervention dans différents contextes. On a également constaté que ces grappes ne sont pas nécessairement spécifiques à la vaccination et peuvent survenir dans plusieurs contextes différents. Enfin, le GACVS a noté que le problème est susceptible d'être exacerbé par la méconnaissance de ces incidents, l'absence d'intervention rapide sur place, le recours trop fréquent à l'hospitalisation et les réactions excessives des prestataires de soins et des administrateurs de programme face à ces manifestations.

Signaux relatifs à la sécurité vaccinale dans la base de données du Centre de pharmacovigilance d'Uppsala

Comme l'avait demandé le GACVS en juin 2015, le Secrétariat a présenté 3 signaux récents de sécurité vaccinale enregistrés par le Centre de pharmacovigilance d'Uppsala (UMC) en avril et juillet 2015. Ces signaux étaient associés aux vaccins contre le PVH et aux troubles de la motilité gastro-intestinale, aux vaccins antirabiques et à l'érythème polymorphe, ainsi qu'à l'apparition d'une pemphigoïde bulleuse chez les nourrissons après vaccination. Sur la base de cette expérience, le GACVS a engagé une discussion sur la procédure à suivre pour examiner les signaux de sécurité vaccinale transmis par l'UMC et sur les critères à adopter pour décider des mesures devant être prises par le Comité.

Au titre du Programme OMS de pharmacovigilance internationale, l'UMC a institué Vigibase, une base de données mondiale à notification spontanée de rapports d'innocuité sur les cas individuels portant sur les produits sanitaires. Dans Vigibase, l'UMC soumet le sous-ensemble de rapports d'innocuité portant

subset of vaccine ICSRs in order to identify disproportions in reporting of pairs of vaccines and health outcomes coded with medical terms using WHO-ART and MedDRA as an alternative as the initial step in its process for signal detection. The process includes the use of vigiMatch, a tool to identify duplicate records, and vigiRank, a tool that incorporates disproportionate reporting as one component, but additionally considers several aspects related to the quality and the content of ICSRs. Cases of signals detected by a screening algorithm are reviewed clinically by a group of experts in pharmacovigilance before their communication to the WHO Programme for the International Drug Monitoring.

Currently, the majority of ICSRs involving vaccines are contributed by the USA and individual European countries. The processes for routine signal detection applied by the US Food and Drug Administration (FDA) in the Vaccine Adverse Events Reporting System (VAERS) data and by the European Medicines Agency (EMA) in Eudravigilance were presented. These processes not only use data from spontaneous reports, but also pre-licensure safety information, the medical literature and other sources to detect signals which are considered hypotheses to be verified and further evaluated.

In a presentation on statistical methods for signal detection, the usefulness of the UMC database and of the UMC processes for the detection of vaccine safety signals was emphasized. The limitations of the use of disproportionality analyses on their own to detect signals from large databases were highlighted, and it was suggested that statistical methods will rarely provide strong evidence of causality but are justified for signal detection that may require additional evaluation. It was noted that adverse events following immunization represent about 8.5% of all reports present in Vigibase.

The GACVS concluded that signals documented by the UMC provide useful information in monitoring the safety of vaccines from worldwide sources. It was proposed that a strengthened process of collaboration with UMC would allow use of the expertise on vaccine safety available within the GACVS and partner agencies for the review of this information before it is communicated to the network of pharmacovigilance centres and to vaccine manufacturers. This review should take into account the limitations of signal detection methods along with the reviews performed routinely by the FDA and EMA, given their extensive experience and access to more complete information with the ICSRs they receive and that may not all be shared with UMC. The GACVS Secretariat will liaise with UMC to identify mechanisms for such collaboration.

RTS,S malaria vaccine

GACVS received an update on the recommendations made about use of the RTS,S/AS01 vaccine following the joint meeting of the WHO Strategic Advisory Group of Experts on Immunization (SAGE) and the Malaria Policy

sur les vaccins à un algorithme bayésien pour identifier les notifications disproportionnées de paires vaccins-issues sanitaires, codées selon la terminologie médicale WHO-ART et MedDRA à titre d'alternative pour la première étape du processus de détection des signaux. Ce processus s'appuie sur l'utilisation de vigiMatch, un outil d'identification des doublons, et de vigiRank, une méthode dont l'une des composantes consiste à identifier les notifications disproportionnées, mais qui tient également compte d'autres aspects liés à la qualité et au contenu des rapports. Les cas correspondant aux signaux repérés par l'algorithme de détection font ensuite l'objet d'un examen clinique par un groupe d'experts en pharmacovigilance avant d'être communiqués au Programme OMS de pharmacovigilance internationale.

À l'heure actuelle, la majorité des rapports d'innocuité portant sur les vaccins proviennent des États-Unis et de pays européens. Les procédures utilisées pour la détection systématique des signaux par la *Food and Drug Administration* des États-Unis (FDA) à partir des données du Vaccine Adverse Events Reporting System (VAERS) et par l'Agence européenne des médicaments (EMA) dans le cadre d'Eudravigilance ont été présentées. Ces procédures exploitent non seulement les données des notifications spontanées, mais aussi les informations sur l'innocuité préhomologation et les données issues de publications médicales et d'autres sources pour détecter les signaux qui représentent des hypothèses à vérifier et à évaluer.

Une présentation sur les méthodes statistiques de détection des signaux a souligné l'utilité de la base de données et des procédures de l'UMC pour la détection des signaux relatifs à la sécurité vaccinale. L'accent a été mis sur l'insuffisance des seules analyses de la disproportionalité pour détecter les signaux à partir de grandes bases de données et sur le fait que les méthodes statistiques ne fournissent que rarement des indications solides de causalité, étant toutefois justifiées pour détecter les signaux à soumettre éventuellement à une évaluation complémentaire. Il a été observé que les manifestations postvaccinales indésirables représentent environ 8,5% de tous les rapports de Vigibase.

Le GACVS a conclu que les signaux enregistrés par l'UMC fournissent des informations utiles à la surveillance de l'innocuité des vaccins, dans le monde entier. Il a proposé de renforcer la collaboration avec l'UMC afin de tirer parti de l'expertise disponible au sein du GACVS et des agences partenaires en matière de sécurité vaccinale pour examiner ces informations avant qu'elles ne soient communiquées au réseau de centres de pharmacovigilance et aux fabricants de vaccins. Cet examen devra tenir compte des limites inhérentes aux méthodes de détection des signaux, ainsi que des analyses systématiques réalisées par la FDA et l'EMA, compte tenu de la vaste expérience de ces agences et de leur accès à des informations plus complètes, issues des rapports qui leur sont transmis sans être nécessairement partagés avec l'UMC. Le Secrétariat du GACVS assurera la liaison avec l'UMC pour définir les mécanismes de cette collaboration.

Vaccin antipaludique RTS,S

Le GACVS a pris connaissance des dernières recommandations relatives à l'utilisation du vaccin RTS,S/AS01 suite à la réunion conjointe du Groupe stratégique consultatif d'experts sur la vaccination (SAGE) et du Comité de pilotage de la politique de

Advisory Committee (MPAC) in October 2015.[3] The key recommendation was that large pilot studies of a 4-dose schedule be implemented in a staged manner to address remaining questions concerning efficacy and safety.

GACVS reviewed the safety signals assessed in previous meetings which included an identified risk of generalized convulsions shortly after vaccination and a signal of a potential risk of meningitis of various etiologies. An additional signal had emerged since the June 2015 meeting: a re-analysis of the data demonstrated that in children first vaccinated at 5–17 months of age, an increased number of "cerebral malaria" cases – defined with a highly sensitive but poorly specific case definition as *P. falciparum* asexual parasitaemia of >5000 per mL, a Blantyre Coma Score ≤2, and haemoglobin >5 gm/dL, with or without comorbidities – occurred in the RTS,S groups compared to the controls. In total there were 43 cerebral malaria cases in the RTS,S/AS01 study arms compared to 10 in the control group (2:1 randomization, post-hoc p-value = 0.03). These cases had little overlap with the meningitis cases. The increased number of cerebral malaria cases in the RTS,S group does not explain the severe malaria rebound effect (i.e. the excess of severe malaria cases seen towards the end of the trial in children who did not receive a 4th dose). The majority of cases classified as severe malaria, and most of the excess cases, were associated with other severe disease markers (prostration, respiratory distress, seizures, hypoglycaemia, etc.) rather than Blantyre coma score ≤2. The numerical excess of cerebral malaria was in an unplanned subgroup analysis and its significance relative to RTS,S vaccination is currently unclear. This finding may be due to chance or represent a real effect. GACVS agreed that this was a potential safety signal requiring further evaluation.

GACVS was also made aware of an additional analysis produced for the SAGE/MPAC meeting which provided numbers on all-cause mortality by gender and study arm. Combining across age groups and RTS,S/AS01 study arms the all-cause mortality rate was slightly lower in the RTS,S/AS01 arms than in the control arm in males (ratio of deaths 95:56 with 2:1 randomization, post hoc p-value≈0.34) but about 2-fold higher in females (123:33 with 2:1 randomization, post-hoc p-value≈0.001), largely due to the low female mortality in the control arm (the female mortality in the RTS, S/AS01 arm was similar to male mortality in control and vaccine arms). Patients in the control arm received 3 doses of inactivated rabies vaccine for the primary series and meningococcal C vaccine for those in the booster arm. GACVS also noted that overall mortality in the trial was much lower than the background mortality in the trial area as is often seen in clinical trials. Given this gender disparity in deaths by RTS,S/AS01 and the control arms in this post-hoc analysis, GACVS agreed this also represents a potential safety

[3] See No. 50, 2015, pp. 681–700.

lutte antipaludique (MPAC) en octobre 2015.[3] La recommandation principale concernait la mise en œuvre progressive d'études pilotes à grande échelle sur un schéma d'administration à 4 doses pour répondre aux questions restantes concernant l'efficacité et l'innocuité du vaccin.

Le GACVS a passé en revue les signaux de sécurité vaccinale évalués lors des réunions précédentes, portant notamment sur un risque identifié de convulsions généralisées peu après la vaccination et un risque potentiel de méningite d'étiologies diverses. Un autre signal a été détecté depuis la réunion de juin 2015: chez les enfants dont la première vaccination a été administrée entre l'âge de 5 et 17 mois, une ré-analyse des données à montré que par rapport aux groupes témoins, les groupes RTS,S présentaient un nombre accru de cas de «neuropaludisme» – caractérisés, selon une définition de cas hautement sensible mais peu spécifique, par une parasitémie asexuée à *P. falciparum* >5000 par ml, un score de coma de Bantyre ≤2 et un taux d'hémoglobine >5 g/dl, avec ou sans comorbidités. Au total, 43 cas de neuropaludisme ont été signalés dans les bras de l'étude recevant le RTS,S/AS01, contre 10 dans le groupe témoin (randomisation 2:1, valeur de p post-hoc = 0,03). Ces cas ne présentaient que peu de chevauchement avec les cas de méningite. Le nombre accru de cas de neuropaludisme dans le groupe recevant le RTS,S n'explique pas l'effet de rebond du paludisme grave (c'est-à-dire l'excès de cas graves de paludisme observés vers la fin de l'essai chez les enfants n'ayant pas reçu de 4e dose). La plupart des cas qualifiés de paludisme grave et la majeure partie de l'excès de cas observé étaient associés à d'autres marqueurs de maladie grave (prostration, détresse respiratoire, convulsions, hypoglycémie, etc.) plutôt qu'à un score de coma de Blantyre ≤2. L'excès numérique des cas de neuropaludisme s'est manifesté lors d'une analyse en sous-groupes non prévue au protocole et sa signification vis-à-vis de la vaccination par le RTS,S n'est pas encore claire. Ce résultat peut être le fait du hasard ou refléter un effet réel. Le GACVS a convenu qu'il s'agit d'un signal de sécurité potentiel méritant d'être évalué de manière plus approfondie.

Le GAVCS a également pris connaissance d'une autre analyse, effectuée pour la réunion SAGE/MPAC, indiquant les taux de mortalité, toutes causes confondues, selon le sexe et le bras de l'étude. Sur l'ensemble des tranches d'âge et des bras de l'étude RTS,S/AS01, le taux de mortalité toutes causes confondues était légèrement plus faible dans les bras ayant reçu le RTS,S/AS01 que dans le bras témoin chez les sujets de sexe masculin (rapport de 95:56 décès avec une randomisation 2:1, valeur p post-hoc≈0,34), mais environ 2 fois plus élevé chez les sujets de sexe féminin (123:33 avec une randomisation 2:1, valeur p post-hoc≈0,001), ce qui s'explique en grande partie par le faible taux de mortalité féminine dans le bras témoin (la mortalité féminine dans le bras RTS,S/AS01 était comparable à la mortalité masculine dans les groupes vaccinés et témoins). Les patients du groupe témoin ont reçu 3 doses de vaccin antirabique inactivé pour la série de primovaccination et le vaccin contre le méningocoque C dans le groupe recevant une dose de rappel. Le GACVS a également constaté que le taux global de mortalité des sujets participant à l'essai était bien inférieur à la mortalité générale de la population dans la zone concernée, comme c'est souvent le cas dans les études cliniques. Au vu de l'écart de

[3] Voir N° 50, 2015, p. 681-700.

signal and noted that SAGE/MPAC have recommended that gender-specific all-cause mortality be assessed in the pilot studies of a 4-dose schedule.

GACVS recommended that sub-committee members be involved in the safety aspects of the design of the pilot studies given these signals which require further assessment. During the course of those pilot implementations, the preparation of a guidance manual on safety assessment post licensure will be placed on hold.

Safety of HPV vaccines

Since first being licensed at the beginning of 2006, >200 million doses of HPV vaccines have been distributed globally. WHO recommends that HPV vaccines be introduced into national immunization programmes provided that: prevention of cervical cancer and/or other HPV-related diseases constitute a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost-effectiveness of vaccination strategies in the country or region is considered.[4] The GACVS has systematically investigated safety concerns raised about HPV vaccines and has issued several reports in this regard.[5] To date, GACVS has not found any safety issue that would alter its recommendations for the use of the vaccine.

GACVS reviewed data from a recent retrospective cohort study from the French National Agency for Medicines and Health Products Safety on autoimmune conditions following HPV vaccination.[6] This large study of >2 million girls showed a similar incidence in the vaccinated and unvaccinated populations for all conditions studied, with the exception of Guillain-Barre syndrome where an increased risk was identified, mainly focused within 3 months after vaccination. This risk in the first few months after vaccination was very small (~1 per 100 000 vaccinated children) and has not been seen in other smaller studies. Additional studies in adequately sized populations will help evaluate this finding and, if confirmed, better assess the magnitude of an eventual risk. This risk, which is small, if it exists at all, needs to be seen in the context of the long-lasting cancer-prevention benefits of HPV infection.

In addition, concerns about complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) following HPV vaccination have been

[4] See No. 43, 2014, pp. 465–492.

[5] See http://www.who.int/vaccine_safety/committee/topics/hpv/en/

[6] Agence nationale de sécurité des medicaments et des produits de santé. Vaccins anti-HPV et risque de maladies autoimmunes: étude pharmacoépidémiologique. http://ansm.sante.fr/content/download/80841/1023043/version/1/file/Ansm_Gardasil-Hpv2_Rapport_Septembre-2015.pdf

mortalité observé entre les sujets féminins et masculins dans le bras RTS,S/AS01 et le bras témoin lors de l'analyse post-hoc, le GACVS a convenu qu'il s'agit également d'un signal de sécurité potentiel, ajoutant que le SAGE et le MPAC ont recommandé que la mortalité toutes causes confondues soit évaluée en fonction du sexe des participants lors des études pilotes sur le schéma d'administration à 4 doses.

Compte tenu de ces signaux, qui exigent une évaluation approfondie, le GACVS a recommandé que des membres du sous-comité prennent part aux activités traitant de la sécurité lors de la conception des études pilotes. Durant la mise en œuvre de ces études pilotes, la préparation d'un manuel d'orientation sur l'évaluation de l'innocuité après homologation sera mise en attente.

Innocuité des vaccins contre le PVH

Depuis la première homologation du vaccin contre le PVH au début 2006, >200 millions de doses ont été distribuées à l'échelle mondiale. L'OMS recommande l'introduction des vaccins anti-PVH dans les programmes nationaux de vaccination sous réserve que les conditions suivantes soient réunies: la prévention du cancer du col de l'utérus et/ou d'autres maladies liées au PVH constituent une priorité de santé publique; l'introduction du vaccin est réalisable sur le plan programmatique; un financement durable peut être obtenu; et le rapport coût/efficacité des stratégies vaccinales dans le pays ou la région concernée est pris en compte.[4] Le GACVS a systématiquement étudié les inquiétudes émises sur la sécurité des vaccins anti-PVH et a publié plusieurs rapports à ce sujet.[5] Le GACVS n'a identifié à ce jour aucun problème de sécurité vaccinale justifiant une modification de ses recommandations concernant l'utilisation du vaccin.

Le GACVS a examiné les données issues d'une récente étude rétrospective de cohorte de l'Agence nationale française de sécurité du médicament et des produits de santé, portant sur les risques de maladies auto-immunes après la vaccination contre le PVH.[6] Cette vaste étude, comptant >2 millions de jeunes filles, a conclu que l'incidence de toutes les maladies étudiées était comparable entre les populations vaccinées et non vaccinées, à l'exception du syndrome de Guillain-Barré pour lequel un risque accru a été identifié, essentiellement au cours des 3 premiers mois suivant la vaccination. Ce risque observé dans les premiers mois après vaccination était très faible (~1 enfant vacciné sur 100 000) et ne s'est pas manifesté dans d'autres études de plus petite taille. De nouvelles études auprès de populations de taille convenable permettront d'analyser ce résultat et, s'il est confirmé, de mieux estimer l'ampleur du risque éventuel. Ce risque, s'il existe, est faible et doit être évalué à la lumière des avantages durables procurés par la vaccination en termes de prévention des cancers résultant d'une infection par le PVH.

En outre, en certains endroits, des inquiétudes ont été suscitées par des cas de syndrome douloureux régional complexe (SDRC) et de syndrome de tachycardie orthostatique posturale (STOP)

[4] Voir N° 43, 2014, p. 465-492.

[5] Voir http://www.who.int/vaccine_safety/committee/topics/hpv/fr/.

[6] Agence nationale de sécurité du médicament et des produits de santé. Vaccins anti-HPV et risque de maladies auto-immunes: étude pharmaco-épidémiologique. http://ansm.sante.fr/content/download/80841/1023043/version/1/file/Ansm_Gardasil-Hpv2_Rapport_Septembre-2015.pdf.

raised in certain geographic locations. These are both disorders of unclear and possibly heterogeneous etiology and the epidemiology of both conditions is not well characterized. CRPS is a chronic, painful condition usually affecting a single limb that typically follows an episode of trauma or immobilization of a limb. The onset of symptoms of CRPS is difficult to define and is usually recognised among patients with continuing pain long after the trauma. POTS is characterized by an abnormally large and sustained increase in heart rate when changing from a lying down to an upright position. This excessive heart rate increase is usually accompanied by a range of symptoms of orthostatic intolerance. Several clinical and epidemiological features contribute to POTS being especially challenging to study. Onset of POTS may be extremely difficult to ascertain retrospectively. POTS is probably relatively common in young adolescents, may be relatively infrequently diagnosed, and may be difficult to distinguish from the normal range of physiologic responses in this age group. Additionally, syncope is a common adverse event in response to vaccination, especially among adolescents, which may lead to differential ascertainment of POTS in vaccinated and unvaccinated populations.

Despite the difficulties in diagnosing or fully characterizing CRPS and POTS, reviews of pre- and post-licensure data provide no evidence that these syndromes are associated with HPV vaccination. Some symptoms of CRPS and POTS also overlap with symptoms of chronic fatigue syndrome for which a published observational study reported no association with HPV vaccines.[7]

Although some cases of POTS reports were severe and long-lasting, the prognosis of POTS with symptomatic management is usually favourable, and symptoms in adolescents often resolve over time. Given the lack of specificity of some of the symptoms reported following HPV vaccination, clinicians are encouraged to refer severely affected patients to physicians familiar with these syndromes for diagnosis and management. Prompt diagnosis and management by experienced clinicians may avoid harmful and unnecessary medical interventions and promote a prompt return to normal activities.

The circumstances in Japan, where the occurrence of chronic pain and other symptoms in some vaccine recipients has led to suspension of the proactive recommendation for routine use of HPV vaccine in the national immunization programme, warrants additional comment. Review of clinical data by the national expert committee led to a conclusion that symptoms were not related to the vaccine, but it has not been possible to reach consensus to resume HPV vaccination. As a result, young women are being left vulnerable to HPV-related cancers that could be prevented. As GACVS has noted previously, policy decisions based on weak evidence,

suite à la vaccination anti-PVH. Il s'agit de 2 troubles d'étiologie incertaine et potentiellement hétérogène, dont l'épidémiologie est mal caractérisée. Le SDRC est une affection chronique et douloureuse, souvent localisée au niveau d'un membre unique, faisant généralement suite à un traumatisme ou à une immobilisation du membre en question. L'apparition des symptômes de SDRC est difficile à définir et est souvent reconnue lorsqu'un patient continue de ressentir de la douleur longtemps après le traumatisme. Le STOP se caractérise par une augmentation anormale et durable de la fréquence cardiaque lors du passage d'une position couchée à une position verticale. Cette hausse excessive de la fréquence cardiaque est généralement accompagnée de divers symptômes d'intolérance orthostatique. Plusieurs caractéristiques cliniques et épidémiologiques font du STOP un syndrome particulièrement difficile à étudier. La survenue des symptômes du STOP peut être extrêmement difficile à constater rétrospectivement. Ce syndrome, probablement assez courant chez les jeunes adolescents mais relativement peu souvent diagnostiqué, peut être difficile à distinguer des diverses réponses physiologiques normales de cette tranche d'âge. De plus, la syncope est une manifestation indésirable courante après la vaccination, surtout à l'adolescence, ce qui risque d'entraîner un écart de constatation des cas de STOP entre les populations vaccinées et non vaccinées.

Malgré les difficultés de diagnostic et de caractérisation du SDRC et du STOP, l'examen des données préhomologation et posthomologation n'apporte aucune preuve d'un lien entre ces syndromes et la vaccination anti-PVH. Le SDRC et le STOP ont certains symptômes en commun avec le syndrome de fatigue chronique, pour lequel une étude d'observation publiée n'a trouvé aucune association avec les vaccins anti-PVH.[7]

Bien que certains cas sévères et durables de STOP aient été signalés, le pronostic de ce syndrome est généralement favorable avec une prise en charge symptomatique, et les symptômes disparaissent souvent avec le temps chez les adolescents. Compte tenu du manque de spécificité de certains des symptômes signalés après la vaccination contre le PVH, il est recommandé aux cliniciens d'orienter les patients les plus gravement touchées vers des médecins connaissant bien ces syndromes pour le diagnostic et la prise en charge. Un diagnostic et une prise en charge rapides par des cliniciens expérimentés permettent d'éviter les interventions nocives et inutiles et favorisent une reprise rapide des activités normales.

La situation au Japon, où la recommandation proactive d'administration systématique du vaccin anti-PVH dans le cadre du programme national de vaccination a été suspendue suite à la survenue de douleurs chroniques et d'autres symptômes chez certaines personnes vaccinées, mérite de plus amples commentaires. Après examen des données cliniques, le comité national d'experts a conclu que les symptômes n'étaient pas liés au vaccin, mais un consensus sur la reprise de la vaccination contre le PVH n'a pas pu être trouvé. Par conséquent, des jeunes femmes demeurent exposées au risque évitable de cancer lié au PVH. Comme l'a déjà indiqué le GACVS, les décisions politiques fondées sur des éléments peu probants menant à l'abandon de

[7] Donegan K, Beau-Lejdstrom R, King B, et al. Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. Vaccine 2013; 31:4961–4967.

[7] Donegan K, Beau-Lejdstrom R, King B, et al. Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. Vaccine 2013; 31:4961–4967.

leading to lack of use of safe and effective vaccines, can result in real harm.[8]

Continued pharmacovigilance will be important in order to ensure that concerns related to the use of HPV vaccines can be addressed with the best possible evidence. The impact of HPV vaccines on HPV-related clinical outcomes, including precancerous lesions, is well established. The greatest health benefit globally is anticipated in countries without routine cervical cancer screening, where the vaccine is yet to be introduced. Enhanced spontaneous reporting of adverse events following immunization should be put in place to ensure that those who could benefit the most from the intervention are vaccinated with adequate safety monitoring.

Influenza A (H1N1) 2009 pandemic vaccine and narcolepsy

GACVS last reviewed the potential association between 2009 H1N1 influenza vaccine and narcolepsy at the June 2013 meeting.[9] On that occasion it was noted that for the vaccine Pandemrix® there was evidence from several studies of a possible risk in adults which was lower than that seen in children, and that this needed further research to confirm the strength of the observed association and the magnitude of the risk. In addition the need for further research to identify the underlying pathophysiological mechanism was highlighted.

Since the last review a Canadian study has been published assessing the risk of narcolepsy following the use of another monovalent AS03 adjuvanted vaccine Arepanrix®.[10] This vaccine was produced in a separate facility from Pandemrix® with different processes for inactivation and purification. The cohort study, which had a much lower background incidence of narcolepsy than reported in the studies in Europe and which only had the power to assess all ages combined, found a much smaller relative and attributable risk with this vaccine. Further data on the Pandemrix®-narcolepsy risk in adults from a study in England submitted for publication were also reviewed. This study also found an association in adults which was of smaller magnitude than that seen in children.

Following recent publications critiquing the published narcolepsy studies and highlighting possible biases[11, 12] GACVS examined how the studies had dealt with this. The main issue was whether media attention led to ascertainment bias. Most studies did address this potential bias by restricting key analyses to periods prior to media attention. Suggestions in the critiques that there

vaccins efficaces et sans danger peuvent avoir des conséquences préjudiciables.[8]

La pharmacovigilance continuera de jouer un rôle crucial, permettant d'examiner les inquiétudes relatives aux vaccins anti-PVH en s'appuyant sur les meilleurs éléments de preuve possibles. L'effet des vaccins anti-PVH sur les conséquences cliniques liées au PVH, y compris les lésions précancéreuses, est bien établi. À l'échelle mondiale, les pays susceptibles d'en tirer le plus grand bénéfice sur le plan sanitaire sont ceux où le dépistage du cancer du col utérin n'est pas systématique; or le vaccin n'a pas encore été introduit dans ces pays. Il convient d'améliorer la notification spontanée des manifestations postvaccinales indésirables afin que les personnes susceptibles de tirer le plus grand avantage de la vaccination puissent être vaccinées dans des conditions adéquates de surveillance de l'innocuité.

Vaccin contre la grippe pandémique A(H1N1) de 2009 et narcolepsie

Le dernier examen du GACVS concernant le lien entre le vaccin contre la grippe H1N1 de 2009 et la narcolepsie remonte à la réunion de juin 2013.[9] À cette occasion, le Comité avait constaté, pour le vaccin Pandemrix®, que plusieurs études signalaient un risque éventuel chez l'adulte, plus faible que le risque observé chez l'enfant. Le Comité avait convenu que de nouveaux travaux de recherche étaient nécessaires pour confirmer la force de l'association observée et l'ampleur du risque et pour identifier les mécanismes physiopathologiques sous-jacents.

Depuis ce dernier examen, une étude canadienne, portant sur le risque de narcolepsie suite à l'utilisation d'Arepanrix®, un autre vaccin monovalent avec l'adjuvant AS03, a été publiée.[10] Ce vaccin avait été produit dans un site distinct et selon des procédés d'inactivation et de purification différents de Pandemrix®. Cette étude de cohorte, caractérisée par une incidence de fond de narcolepsie beaucoup plus faible que dans les études réalisées en Europe et ne permettant qu'une évaluation tous âges confondus, a mis en évidence un risque relatif et attribuable bien plus faible avec ce vaccin. Le GACVS a également examiné d'autres données, provenant d'une étude réalisée en Angleterre et non encore publiée, portant sur le risque de narcolepsie associé à Pandemrix® chez l'adulte. Cette étude a également conclu à une association chez l'adulte, plus faible que chez l'enfant.

Suite à la publication récente d'articles critiques à l'égard des études publiées sur la narcolepsie, évoquant plusieurs biais éventuels,[11, 12] le GACVS a examiné la manière dont ils avaient été abordés dans les études concernées. Le problème principal avait trait à la possibilité que l'attention médiatique portée à la question ait pu entraîner un biais de constatation des cas. La plupart des études se sont attachées à corriger ce biais

[8] See http://www.who.int/vaccine_safety/committee/topics/hpv/GACVS_Statement_HPV_12_Mar_2014.pdf

[9] See No. 29, 2013, pp. 309–312.

[10] Montplaisir J, Petit D, Quinn MJ, et al. Risk of narcolepsy associated with inactivated adjuvanted (AS03) A/H1N1 (2009) pandemic influenza vaccine in Quebec. PLoS One. 2014 Sep 29;9(9):e108489.

[11] Verstraeten T1, Cohet C2, Dos Santos G3, et al. Pandemrix™ and narcolepsy: A critical appraisal of the observational studies. Hum Vaccin Immunother. 2015 Sep 17:1–7.

[12] Sturkenboom MC. The narcolepsy-pandemic influenza story: can the truth ever be unraveled? Vaccine. 2015 Jun 8;33 Suppl 2:B6-B13.

[8] Voir http://www.who.int/vaccine_safety/committee/topics/hpv/GACVS_Statement_HPV_12Mar2014_FR.pdf.

[9] Voir N° 29, 2013, p. 309-312.

[10] Montplaisir J, Petit D, Quinn MJ, et al. Risk of narcolepsy associated with inactivated adjuvanted (AS03) A/H1N1 (2009) pandemic influenza vaccine in Quebec. PLoS One. 2014 Sep 29;9(9):e108489.

[11] Verstraeten T1, Cohet C2, Dos Santos G3, et al. Pandemrix™ and narcolepsy: A critical appraisal of the observational studies. Hum Vaccin Immunother. 2015 Sep 17:1–7.

[12] Sturkenboom MC. The narcolepsy-pandemic influenza story: can the truth ever be unraveled? Vaccine. 2015 Jun 8;33 Suppl 2:B6-B13.

was evidence of longer delays from onset of diagnosis in unvaccinated individuals when compared to vaccinated individuals were found to be based on misinterpretation of these delays. Overall the studies to date have produced consistent results for the risk following Pandemrix® despite various sources of data and study designs.

Several hypotheses have been proposed to explain the pathophysiological mechanism of narcolepsy following adjuvanted 2009 H1N1 vaccination. A differential content of viral nucleoproteins has been observed between Pandemrix and Arepanrix[13, 14] that occurred in the production process. The high immunogenicity of the adjuvanted vaccine has also been proposed as a co-factor for producing immune-mediated damage to hypocretin or hypocretin receptors in the hypothalamus. Narcolepsy has been known since 2000 to be due to low levels of this neuropeptide in the cerebrospinal fluid. The autoimmune nature of narcolepsy has not yet been directly demonstrated but is suggested by a close association with HLA type DQB1*0602. Cross-reactivity of T-cells and antibodies to vaccine antigens and hypocretin receptors has been documented but is also found among healthy controls. GACVS therefore concluded that at this stage, the evidence for a clear cross-reactive pathogenic mechanism remains limited.

GACVS discussed the fact that the association of childhood narcolepsy with Pandemrix could not have been predicted and therefore could not have been put on the list of possible adverse effects of special interest used in influenza vaccine pharmacovigilance post licensure. In addition, there is a possibility that without the high immunization coverage achieved in Finland and Sweden and the vigilance of individual neurologists, the signal could have been missed. The committee also noted that despite the very low incidence of narcolepsy, signal detection was facilitated in this instance by the greatly elevated risk in a relatively short post-vaccination window period.

Large databases for signal strengthening such as PRISM (Post-licensure Rapid Immunization Safety Monitoring system) and the Vaccine Safety DataLink in the USA are seen as important tools to be encouraged in other settings. However, care needs to be taken in pooling data from different databases with different variables and whose potential biases and confounders may operate to obscure a signal. Separate analyses should also be carried out. The existence of new EMA guidelines on good pharmacovigilance practices for all vaccines in general published in December 2013 were also highlighted at the meeting.[15]

potentiel en limitant les analyses essentielles aux périodes antérieures à l'attention médiatique. Selon les critiques, certaines données semblaient par ailleurs indiquer que le délai entre l'apparition des symptômes et le diagnostic avait été plus long chez les sujets non vaccinés que chez les sujets vaccinés. Il a été déterminé que ces affirmations étaient fondées sur une interprétation erronée des délais en question. De manière générale, les études menées à ce jour ont produit des résultats cohérents quant au risque associé à Pandemrix®, bien que reposant sur des sources de données et des schémas d'étude différents.

Plusieurs hypothèses ont été émises pour expliquer le mécanisme physiopathologique de survenue de la narcolepsie suite à l'administration du vaccin adjuvanté contre la grippe H1N1 de 2009. Une différence de contenu en nucléoprotéines virales, survenue lors du processus de production, a été observée entre Pandemrix et Arepanrix.[13, 14] Une hypothèse selon laquelle la forte immuno-génicité du vaccin adjuvanté serait un cofacteur de dégradation à médiation immunitaire de l'hypocrétine ou des récepteurs de l'hypocrétine dans l'hypothalamus a également été proposée. On sait depuis 2000 que la narcolepsie est due à un taux insuffisant de ce neuropeptide dans le liquide céphalorachidien. L'origine auto-immune de la narcolepsie n'a pas encore été directement démontrée, mais est suggérée par son association étroite au groupe HLA de type DQB1*0602. Une réactivité croisée des lymphocytes T et des anticorps contre les antigènes vaccinaux et les récepteurs de l'hypocrétine a été démontrée, mais elle est également présente chez les témoins sains. Le GACVS a donc conclu qu'à ce stade, les preuves d'un mécanisme pathogène clair de réaction croisée restent limitées.

Le GACVS a précisé que l'association entre la narcolepsie de l'enfant et le Pandemrix était imprévisible et ne pouvait donc pas être incluse dans la liste des effets indésirables d'intérêt spécifique potentiels dans le cadre de la pharmacoviligance posthomologation des vaccins antigrippaux. De plus, si la couverture vaccinale n'avait pas été aussi élevée en Finlande et en Suède et si les neurologues n'avaient pas fait preuve d'une si grande vigilance individuelle, le signal n'aurait peut-être pas été détecté. Le Comité a également observé qu'en dépit de la très faible incidence de la narcolepsie, la détection du signal a été favorisée, dans le cas présent, par une forte élévation du risque dans une période postvaccinale relativement courte.

Les grandes bases de données comme PRISM (Post-licensure Rapid Immunization Safety Monitoring system) et Vaccine Safety DataLink aux États-Unis permettent le renforcement des signaux et leur emploi devrait être encouragé dans d'autres contextes. Il faut toutefois faire preuve de prudence lorsque les données sont regroupées à partir de diverses bases de données dont les variables sont différentes et dont les biais et facteurs de confusion potentiels risquent de brouiller les signaux. Il convient également d'effectuer des analyses distinctes. Le Comité a par ailleurs rappelé qu'en décembre 2013, l'EMA a publié de nouvelles lignes directrices générales sur les bonnes pratiques de pharmacovigilance applicables à tous les vaccins.[15]

[13] Varaala O, Vuorela A, Partinen M, et al. Antigenic differences between AS03 adjuvanted influenza A (H1N1) pandemic vaccines: implications for pandemrix-associated narcolepsy risk. PLoS One. 2014 Dec 15;9(12):e114361.

[14] Ahmed SS, Volkmuth W, Duca J, et al. Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2. Sci Transl Med. 2015 Jul 1;7(294):294ra105.

[15] See http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c

[13] Varaala O, Vuorela A, Partinen M, et al. Antigenic differences between AS03 adjuvanted influenza A (H1N1) pandemic vaccines: implications for pandemrix-associated narcolepsy risk. PLoS One. 2014 Dec 15;9(12):e114361.

[14] Ahmed SS, Volkmuth W, Duca J, et al. Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2. Sci Transl Med. 2015 Jul 1;7(294):294ra105.

[15] Voir http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c.

Safety of smallpox vaccines

GACVS had previously considered the safety of smallpox vaccination.[16] The Committee was provided with updated safety information for 1st, 2nd and 3rd generation smallpox vaccines in order to make informed decisions regarding emergency smallpox vaccine stockpiling and future use. The safety update also included an overview of the safety of smallpox vaccines used in the smallpox eradication efforts. Detailed safety information was provided for the currently licensed replicating 2nd generation ACAM2000 and the non-replicating 3rd generation Imvanex/Imvamune smallpox vaccines.

ACAM2000®, manufactured by Sanofi Pasteur Biologics, LLC is a live vaccinia virus smallpox vaccine derived by plaque purification from previously licensed calf lymph produced vaccine (Dryvax) and manufactured in Vero cells. It is indicated for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection. ACAM2000 vaccine is currently licensed in the USA, Australia, and Singapore. Serious adverse effects reported from clinical trials with ACAM2000 include myopericarditis and cardiomyopathy. Three safety surveillance studies are ongoing, including a myopericarditis registry to document the natural history of myopericarditis following ACAM2000 vaccination, a prospective cohort study in deployed military personnel, and an enhanced safety surveillance study in military personnel to evaluate the rates of suspected and confirmed myopericarditis in temporal association with ACAM2000 vaccination. Apart from the known signal of myopericarditis observed in these studies, rare serious sequelae, e.g. disseminated vaccinia, *eczema vaccinatum* and encephalopathy, have not been observed. The updated safety information for ACAM2000 did not reveal any new areas of concern after administration to approximately 1 million people.

Imvanex/Imvamune®, manufactured by Bavarian Nordic is a modified vaccinia virus Ankara derived from replication-competent dermal vaccinia strain Ankara attenuated after >570 continuous passages in primary chicken embryo fibroblasts that has undergone 6 rounds of plaque purification and is propagated in serum-free conditions. Due to its high level of attenuation, it is no longer replication-competent in human cell lines. It is indicated for active immunization against smallpox in adults and approved in Europe and Canada. Safety summary data from completed and ongoing clinical trials in which >7600 individuals received the vaccine, including vaccinia naive and experienced populations, HIV positive subjects and persons with atopic dermatitis, showed that the vast majority of events represented local and systemic reactions reported as mild to moderate and resolved rapidly without intervention. The vaccine was well tolerated with no clinically relevant differences between the populations studied. There was one unconfirmed case of "possible acute pericarditis" in the recently completed phase 3 clinical study that

[16] See No. 3, 2004, p. 20.

Innocuité des vaccins antivarioliques

L'innocuité de la vaccination antivariolique avait déjà fait l'objet d'un examen par le GACVS.[16] Des informations actualisées sur la sécurité des vaccins antivarioliques de 1re, 2e et 3e générations ont été présentées au Comité pour favoriser une prise de décisions éclairée quant à la constitution de stocks et l'utilisation future des vaccins antivarioliques. Cette mise à jour contenait également des informations générales sur l'innocuité des vaccins antivarioliques utilisés dans le cadre des efforts d'éradication de la variole. Des informations détaillées de sécurité vaccinale ont été fournies pour le vaccin antivariolique réplicant de 2e génération actuellement homologué, ACAM2000, et le vaccin non réplicant de 3e génération Imvanex/Imvamune.

ACAM2000®, fabriqué par Sanofi Pasteur Biologics, LLC est un vaccin antivariolique à base de virus vivants de la vaccine qui est dérivé, par purification par la méthode des plages, d'un vaccin préalablement homologué, Dryvax, préparé à partir de lymphe de veau et fabriqué dans des cellules Vero. Il est indiqué pour la vaccination active contre la variole chez les personnes exposées à un risque élevé d'infection variolique. Le vaccin ACAM2000 est actuellement homologué aux États-Unis, en Australie et à Singapour. Parmi les effets indésirables graves d'ACAM2000 signalés lors des essais cliniques figurent la myopéricardite et la myocardiopathie. Trois études de surveillance de l'innocuité sont en cours: un registre des cas de myopéricardite pour rendre compte de l'histoire naturelle de la myopéricardite après la vaccination par ACAM2000, une étude de cohorte prospective auprès de militaires déployés, et une étude approfondie de surveillance de la sécurité vaccinale auprès du personnel militaire pour évaluer les taux de myopéricardite soupçonnée et confirmée en rapport temporel avec la vaccination par ACAM2000. Mis à part ce signal connu de myopéricardite observé dans ces études, aucune séquelle grave et rare, telle que vaccine disséminée, eczéma vaccinal ou encéphalopathie, n'a été constatée. Après l'administration d'ACAM2000 à environ 1 million de personnes, les informations de sécurité vaccinale actualisées ne révèlent aucun nouvel élément préoccupant.

Imvanex/Imvamune®, fabriqué par Bavarian Nordic, est un virus modifié de la vaccine Ankara, dérivé d'une souche de la vaccine Ankara dermique capable de se répliquer, atténué par >570 passages continus sur des fibroblastes embryonnaires primaires de poulet, ayant subi 6 cycles de purification par la méthode des plages et propagé dans un milieu sans sérum. En raison de sa forte atténuation, il n'est plus capable de se répliquer dans les lignées cellulaires humaines. Il est indiqué pour la vaccination antivariolique active des adultes et est homologué en Europe et au Canada. Les données de synthèse sur la sécurité vaccinale issues de plusieurs essais cliniques, terminés ou en cours, durant lesquels le vaccin a été administré à >7600 personnes, y compris des sujets qui n'avaient jamais été exposés au virus de la vaccine, des sujets qui l'avaient déjà été, des personnes séropositives pour le VIH et des patients présentant une dermatite atopique, montrent que la grande majorité des manifestations signalées étaient des réactions locales et systémiques d'intensité légère à modérée qui se sont rapidement résorbées, sans intervention. Le vaccin était bien toléré, sans différence cliniquement significative entre les populations étudiées. Un cas non confirmé de «péricardite aiguë éventuelle»,

[16] Voir Nº 3, 2004, p. 20.

was considered possibly vaccine related by the investigator. However, no confirmed case of myopericarditis or any other cardiac inflammatory event in any Imvanex/Imvamune clinical trial was observed.

GACVS noted that overall, no new safety concerns have been observed with the ACAM2000 and Imvanex/Imvamune smallpox vaccines. There is little safety information on these newer smallpox vaccines among pregnant women and it is not known whether the safety profiles of these vaccines differ depending on ethnic background. There are also no data in pediatric subjects and GACVS noted that in the absence of circulating smallpox, these vaccines should not be used in pediatric populations. The vaccines have been shown to be immunogenic and protective against lethal orthopoxvirus challenge in animal models.

GACVS recommended that any use of smallpox vaccines be guided by the anticipated risk versus benefit presented during various outbreak or exposure scenarios. For example, in a situation of a widespread smallpox outbreak, the risks of adverse events following vaccination may be acceptable. While the risk of a widespread smallpox outbreak is low, outbreaks or exposures to other orthopoxviruses that are more limited in size and scope may occur. Under these scenarios, adequate screening procedures may minimize the risks associated with vaccination. ■

considéré par le chercheur comme potentiellement lié à la vaccination, a été signalé lors de la phase 3 de l'essai, récemment menée à bien. Cependant, aucun cas confirmé de myopéricardite ou de toute autre manifestation cardiaque inflammatoire n'a été observé dans l'ensemble des études cliniques sur Imvanex/Imvamune.

Le GACVS a noté que globalement, aucun nouveau problème d'innocuité des vaccins antivarioliques ACAM2000 et Imvanex/Imvamune n'a été observé. On ne dispose que de peu d'informations sur la sécurité de ces nouveaux vaccins antivarioliques chez la femme enceinte et on ne sait pas si leur profil d'innocuité varie en fonction de l'appartenance ethnique. Aucune donnée ne renseigne non plus sur l'utilisation de ces vaccins chez l'enfant; le GACVS a indiqué qu'en l'absence de circulation de la variole, l'administration de ces vaccins aux enfants est à proscrire. L'immuno-génicité et le pouvoir protecteur de ces vaccins contre une inoculation d'épreuve mortelle par les orthopoxvirus ont été démontrés dans des modèles animaux.

Le GACVS a recommandé que toute décision relative à l'utilisation des vaccins antivarioliques soit fondée sur une évaluation des risques anticipés par rapport aux avantages procurés dans divers scénarios de flambée ou d'exposition. Par exemple, en situation de flambée de variole de grande ampleur, les risques de manifestations indésirables postvaccinales peuvent être jugés acceptables. Le risque d'une flambée de variole de grande ampleur est certes faible, mais il est possible que surviennent des flambées ou des expositions à d'autres orthopoxvirus, de taille et de portée plus limitée. Dans de tels scénarios, l'emploi de procédures adéquates de dépistage peut réduire les risques associés à la vaccination. ■

How to obtain the WER through the Internet

(1) WHO WWW server: Use WWW navigation software to connect to the WER pages at the following address: **http://www.who.int/wer/**

(2) An e-mail subscription service exists, which provides by electronic mail the table of contents of the WER, together with other short epidemiological bulletins. To subscribe, send a message to **listserv@who.int**. The subject field should be left blank and the body of the message should contain only the line subscribe wer-reh. A request for confirmation will be sent in reply.

Comment accéder au REH sur Internet?

1) Par le serveur Web de l'OMS: A l'aide de votre logiciel de navigation WWW, connectez-vous à la page d'accueil du REH à l'adresse suivante: **http://www.who.int/wer/**

2) Il existe également un service d'abonnement permettant de recevoir chaque semaine par courrier électronique la table des matières du REH ainsi que d'autres bulletins épidémiologiques. Pour vous abonner, merci d'envoyer un message à **listserv@who.int** en laissant vide le champ du sujet. Le texte lui même ne devra contenir que la phrase suivante: subscribe wer-reh.

Monthly report on dracunculiasis cases, January–November 2015

In order to monitor the progress accomplished towards dracunculiasis eradication, district-wise surveillance indicators, a line list of cases and a line list of villages with cases are sent to WHO by the national dracunculiasis eradication programmes. Information below is summarized from these reports. ■

Rapport mensuel des cas de dracunculose, janvier-novembre 2015

Afin de suivre les progrès réalisés vers l'éradication de la dracunculose, les programmes nationaux d'éradication de la dracunculose envoient à l'OMS des indicateurs de surveillance des districts sanitaires, une liste exhaustive des cas ainsi qu'une liste des villages ayant signalé des cas. Les renseignements ci-dessous sont résumés à partir de ces rapports. ■

Advances in RSV Vaccine Research and Development - A Global Agenda

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Highlights

- RSV is a significant annual cause of lower respiratory tract illness globally.
- Pediatric and elderly populations are most vulnerable, but no vaccine exists.
- The current state of RSV vaccine research and development is summarized.
- 60 RSV vaccine candidates in development, of which 16 are in Phase 1-3 trials.

Keywords: Respiratory Syncytial Virus, Research and Development, Vaccine

Conflict of Interest: The authors have no conflicts of interests to declare.

Abstract

Respiratory syncytial virus (RSV) is an important cause of viral lower respiratory tract illness in infants and children globally, but no vaccine is currently available to protect these vulnerable populations. Live-attenuated vaccine approaches have been in development for decades, but achieving the appropriate balance between immunogenicity and safety has proven difficult. Immunoprophylaxis with the neutralizing monoclonal antibody palivizumab is limited to high risk infants, but cost requirements for multiple dosing make its use impractical in low- and middle-income countries. A growing number of RSV vaccine candidates using a variety of technologies and targeting diverse populations has emerged in recent years. There are now 60 RSV vaccine candidates in development targeting pediatric as well as elderly populations, and while most are at a preclinical stage, 16 candidates are in clinical development. This article summarizes current RSV vaccine research and development, including an overview of the vaccine platforms being used, the development stage of individual vaccine candidates, and gaps to be addressed to facilitate use of these vaccines to meet global health needs.

Introduction

Respiratory syncytial virus (RSV) is the most important cause of viral lower respiratory tract illness in infants and children globally. It is responsible for one-third of deaths resulting from acute lower respiratory infection (ALRI) in the first year of life.[1] RSV, which is transmitted by direct and indirect contact with nasal or oral secretions, causes repeat infections throughout life and significant disease in pediatric and elderly populations. [2, 3] The pathogen is an enveloped, non-segmented, single-stranded, negative-sense RNA pneumovirus belonging to the family *Paramyxoviridae*. The viral genome consists of 10 genes encoding 11 proteins. The fusion (F) and attachment (G) surface glycoproteins are most important in their ability to induce neutralizing antibodies. [4] The virus circulates seasonally in temperate regions, usually between the late fall and early spring, and lasts three to four months in a community (although timing varies between years and regions and within communities). In tropical regions, the seasonal relationship is less defined with virus detectable year round in some locations.

The annual global burden of RSV is estimated to be 33.8 million new episodes of ALRI in children less than five years old, 3.4 million hospital admissions, and in 2010 253,000 deaths, with most of the fatalities occurring in developing countries. [1, 5] The lack of supportive care contributes to the increased severity and mortality in such settings. The RSV mortality rate is difficult to accurately assess in many countries due to the unavailability and infrequent use of diagnostics. Under-reporting of cases and deaths may also occur because they never come in contact with the local medical system. The RSV Global Estimates Network is in the process of updating morbidity and mortality data, with results expected in 2016.[6] The epidemiology and burden of RSV disease points to several target populations for RSV

vaccines: 1) infants younger than six months of age, who are at highest risk of severe disease; 2) children six months of age and older to prevent disease not only in these children but to help decrease transmission to younger children and the elderly; 3) pregnant women to decrease their transmissibility and to protect newborns by placental antibody transfer; and 4) the elderly, who are also at risk for severe disease. [7] RSV is also a significant concern for other high-risk members of the community, such as pre-term infants, the immunocompromised, and those with pulmonary or congenital heart disease.

Several RSV diagnostic methods are in use today (*i.e.*, cell culture, nucleic acid amplification, and immunofluorescence assays) and are quite heterogeneous in format, specimen preparation, and assay readout. There is only one type of point-of-care diagnostic in use—a rapid antigen detection platform based on immunochromatography. It is generally easy-to-use and provides results within 15 to 30 minutes. This assay tends to have moderate sensitivity but high specificity and yield only qualitative results. However, as infants have higher RSV viral loads, these tests may be a useful option for specific studies (*e.g.*, evaluating vaccine effectiveness in infants). More complex microbiological and molecular laboratory-based platforms have higher sensitivity and specificity, but these tests are more technically challenging and time consuming, requiring experienced laboratory personnel. Molecular methods are being increasingly adopted, however, because they allow for the detection of an array of pathogens, which is useful since many ALRIs are clinically indistinguishable.

While vaccines are among the most cost-effective health interventions for infectious diseases, there are none yet available for RSV. Treatment is usually reserved for patients with severe ALRI and primarily consists of supportive care supplemental oxygen and mechanical ventilation, if needed. Bronchodilators, corticosteroids, and ribavirin have failed to show clear benefit in randomized controlled trials and are not currently recommended for use in many countries. Immunoprophylaxis with the neutralizing monoclonal antibody (mAb) palivizumab is used to a limited extent in the United States and some other high- and middle-income countries to prevent RSV disease in extremely premature infants or those with congenital heart disease. The high cost and requirement for monthly dosing precludes its use in resource-constrained settings.

Feasibility for vaccine development

While there is currently no licensed vaccine for RSV, several observations support the feasibility for RSV vaccine development:

- Primary RSV infection occurs in most infants within the first two years of life, with virtually all children infected by three years of age. Infections recur throughout life but, as natural immunity increases, the disease becomes less severe so that older children and healthy younger adults typically experience a mild upper respiratory illness. Preventing RSV-associated ALRI in the youngest populations, therefore, may be an achievable goal.
- Older adults are at risk for more severe RSV disease. The reason may be multifactorial and could be attributable to underlying cardiac or pulmonary disease and/or immunosenescence.[2]
- The ability of RSV-specific functional antibodies to neutralize viral infection has been demonstrated *in vitro*. Protection has been demonstrated in numerous preclinical models (*i.e.*, mouse, cotton rat, guinea pig, calf, and non-human primate).[8] Furthermore, prophylactic administration of monoclonal or polyclonal antibodies reduces the incidence of severe RSV disease in children.[9] Although serum neutralizing antibody clearly protect against RSV-associated ALRI, other types of immunity (*e.g.*, mucosal antibody cell-mediated immunity) may also contribute and be induced by certain vaccines (*e.g.*, DNA, vector).
- A reduced incidence of RSV ALRI during the first months of life correlates with higher concentrations of RSV-specific maternal antibody.[10]

- Live-attenuated and inactivated virus vaccines have been successfully developed for influenza, a more mutable and antigenically variable respiratory virus than RSV, though both share some virologic and clinical similarities.
- Recent progress defining the RSV prefusion (pre-F) protein structure, and identification of several neutralizing epitopes found only on pre-F, improve the likelihood for making a potent vaccine.

Constraints on RSV vaccine development

The history of RSV vaccine development is notable for the vaccine-enhanced illness that occurred after a formalin-inactivated RSV (FI-RSV) vaccine was administered to seronegative infants in the 1960s.[11-14] The severe lung inflammation, worsened disease, and deaths that occurred in vaccinees raised concerns that other non-replicating RSV vaccines might also predispose infants and RSV-naïve children to aberrant immune responses. However, the immunization of older children with the FI-RSV vaccine did not result in enhanced diseaseas prior infection had primed for a non-deleterious immune response. Proposed mechanisms for disease enhancement include the induction of high titers of non-neutralizing antibodies and Th2-biased cellular immune profile. These types of immunologic responses can lead to immune complex deposition and complement activation and allergic inflammation.[8, 15-17] Enhanced respiratory disease (ERD) has been recapitulated in several animal models, including mice, cotton rats, bovine calves, and African green monkeys.[18-20] The legacy of ERD led to hesitancy from vaccine developers, clinical investigators, and regulators for use of RSV vaccines requiring MHC class II processing in RSV naïve infants. Consequently, only live-attenuated vaccines have been tested for active infant immunization for the last four decades.

General approaches to vaccine development for low- and middle-income country markets

A growing number of RSV vaccine candidates, across multiple platforms, has emerged as of late.

- Live-attenuated RSV vaccines to protect pediatric populations from RSV disease have been in development for decades and do not appear to cause enhanced disease in RSV naïve infants. Recent approaches include engineered viruses that use knowledge of RSV gene function to create ‘knock-out’ viruses that are attenuated but still immunogenic, such as the M2-2 deletion mutant that favors transcription over replication of the genome, leading to more protein production, but limited virus production. Naturally attenuated chimeric viruses combining genes from RSV related viruses such as Sendai, parainfluenza virus, and bovine RSV are also in development.
- Protein-based vaccine approaches (including whole-inactivated virus, subunit antigens that associate to form aggregate particles, and non-particle based subunit antigens) have been developed for protecting elderly populations from severe disease and are often formulated with adjuvant. Particles can display viral proteins, peptides, or neutralizing epitopes with increased density to enhance B cell receptor binding. Particle and protein-subunit vaccines are also being developed for immunization during pregnancy to boost pre-existing immunity to increase transplacental transfer of RSV-specific antibody to infants. Maternal RSV vaccines will likely be more acceptable either as unadjuvanted formulations or adjuvanted only with alum given their history of safe use in this population.
- Replication competent and deficient alphavirus, adenovirus, and modified vaccinia virus Ankara (MVA) vectors encoding RSV surface antigens (including replication-competent and -deficient variations) are being developed for use in infant and pediatric populations. These vectors are intended to express surface proteins in their authentic conformation and processed by MHC class I and class II pathways, thus eliciting robust humoral and cellular immunity.
- Nucleic acid vaccines using either plasmid DNA or messenger RNA encoding RSV antigens are being targeted to protect both pediatric and elderly populations. Combination approaches with DNA and protein are in early development as well and could induce both cellular and humoral immunity.

- A modified version of the D25 monoclonal antibody, which is specific for the neutralizing epitope in antigenic site Ø on the pre-F conformation of RSV fusion (F) protein is being developed for passive prophylaxis in pediatric populations. Genetic modifications that increase potency and half-life may provide protection for an entire RSV season with just a single dose.

A reduction in the incidence and severity of RSV-related ALRI in children younger than five years of age through vaccination in low- and middle-income countries (LMICs) would directly work toward reaching the fourth Millennium Development Goal of reducing child mortality.[5] To achieve this goal, increased awareness and data on RSV disease burden in LMICs is needed, particularly to inform policy makers, regulators, and societies on the potential benefits of vaccine development. In recognition of differing risk and immune profiles, vaccine development will likely have to follow a two-pronged approach that divides the target population into two age groups—younger and older than six months of age.

The incidence of severe RSV disease is highest in infants younger than six months of age.[10, 21] The need for immediate protection and the difficulty of achieving protective efficacy via active immunization in this age group has made maternal immunization and infant passive prophylaxis a priority strategy for protecting young infants. A goal of passive immunoprophylaxis is to provide four to six months of protection with a single dose antibody. A maternal immunization approach would be intended to protect infants for the first two to six months of life. Either of these strategies could be followed with active infant immunization later in life as maternal/passive antibody titers wane.

Numerous live-attenuated and chimeric virus RSV vaccine approaches are being developed. Achieving a proper balance between attenuation (safety) and immunogenicity, as well as genetic stability, has been difficult, although recent advances with recombinantly engineered RSV suggest that this may be feasible.[22] A live vaccine approach targeted to older infants and young children could ultimately complement a maternal/passive immunization approach by protecting these older populations and decreasing transmission of the virus. This approach would bypass the challenge of adequately attenuating live candidates for newborns, and the optimal time for active immunization will depend on the duration of protection afforded by passive immunization.

To reduce the burden of childhood pneumonia, there is strong consensus that focus should be placed on children in their first six months of life, when the risk of severe RSV-associated respiratory disease is highest. To better protect these infants, maternal/passive immunization has become a greater priority. Protection of preterm infants with palivizumab and motavizumab has already been demonstrated and likely will show the same for the next generation of RSV F mAbs in development. A maternal vaccination strategy will be just as important, but, like mAbs, will be limited to the very young and will not protect children beyond four to six months of age. In children with respiratory co-morbidities (*e.g.*, asthma, congenital heart disease, bronchopulmonary dysplasia, cystic fibrosis) an effective RSV vaccine could have significant impact on morbidity. There are reports that up to 50 percent of children who suffer severe RSV bronchiolitis are subsequently diagnosed with asthma. RSV may precipitate the development of asthma or simply be worse in those who are predisposed to asthma.[23] As the mechanism is not understood, the benefit of an RSV vaccine for asthma outcomes is not clear. It is also not well understood how much an RSV vaccine will impact the incidence of secondary respiratory bacterial infection.[24]

Technical and regulatory assessment

Overall, 16 RSV candidates are currently advancing through Phase 1 to Phase 3 clinical trials. The regulatory pathways for RSV vaccines are defined by the following requirements: 1) to establish evidence of protection against RSV disease affecting the very youngest age group; 2) to provide additional ERD safety assurances for an infant vaccine; 3) to generate safety information about the different technologies used (*i.e.*, live, non-replicating, vectored, subunit antigen, extended half-life mAb); and 4) to chart a relatively new pathway if pursuing a maternal indication, which requires immunizing one group and

measuring outcomes in another. A WHO Consultation on Respiratory Syncytial Virus Vaccine Development held 23-24 March 2015 concluded that safety, immunogenicity, and efficacy data in preclinical models (including those that exhibit enhanced disease immunopathology such as the mice, rat, cotton rat, bovine, and baboon models) should be reviewed when considering the advancement of a vaccine candidate into the clinic.[25] In general, safety and immunogenicity studies should first be performed in healthy adults. Early trials that involve seronegative infants should occur in a setting with appropriate facilities for the management of adverse events.[6]

A maternal immunization pathway could start with healthy non-pregnant women of child bearing age, advancing to pregnant women with safety follow up in both mother and infant. The pathway could be accelerated by integrating high and LMIC clinical development, as immunization during pregnancy is more widely accepted and adopted in the developing world. RSV mAb trials may be able to more easily recruit participants given the effectiveness of palivizumab, the existence of an established clinical and regulatory pathway, and the fact that pregnant women will not have to be immunized. However, if the intervention is intended for all, not just children at high risk of severe disease, requirements for showing the mAb is safe and free of any developmental or off-target effects will be high. Pathways for pediatric vaccines using a live-attenuated approach could likewise follow established pre-existing pathways. Development pathways for active infant vaccination using novel vectored approaches could involve age de-escalation safety studies. Since no animal model can absolutely rule out the risk of ERD, advancing vaccine development for vectored vaccines from a seropositive toddler to seronegative infant population involves some level of risk. An NIH/FDA RSV vaccine workshop held June 1-2, 2015 concluded studies in seropositive children would not provide any assurance of safety of subunit or inactivated vaccines for RSV-naïve children, such that there is not clear development path forward for such endeavours. For all clinical development strategies, assessing safety and immunogenicity during co-administration with representative routine vaccines appropriate for the targeted recipients would be necessary.

A commercial RSV IgG ELISA assay from IBL International evaluates immunogenicity of F and G proteins, but does not assess antibody function. Numerous neutralization assay formats have been developed to measure functional antibodies against both RSV A and B subtypes. Harmonization across formats using an international antibody standard (IS) could facilitate the comparison and prioritization of RSV vaccine candidates. A recent survey study across 12 divergent neutralization assay formats testing a common sample panel demonstrated feasibility for harmonization of output by use of a standard. Plans for establishing this IS are being developed by WHO and NIBSC. A binding competition assay is being used to measure antibodies able to compete with palivizumab for binding to the RSV F protein.[26] The palivizumab competitive antibody (PCA) assay shows promise as a means to characterize antibody responses to the RSV F site II neutralizing epitope, one of many neutralizing epitopes on the fusion protein, but does not ensure that the competing antibodies are neutralizing. In passive prophylaxis studies with RSV-IGIV in rodents and infants, high titers of serum neutralizing antibody correlated with protection of the lower respiratory tract.[27-29] Correlates of protection against severe disease in young infants may differ by type of vaccine used and will need to be evaluated in the context of efficacy trials. Regulatory alignment on measurements of disease severity and definitions are important to allow for the advancement of vaccine development programs. Another key component of Phase 3 trials, consensus case definitions/severity scoring systems, are being drafted and discussed.[6] These systems include clinical features that are considered to be objective, easily standardized, generalizable to multiple global settings, and based on generally accepted markers of disease severity. Endpoints for licensure should include safety and reduction of severe disease, but also assess impact on mild or moderate disease. Advancing to WHO prequalification rapidly, once licensure is obtained, is critical because the most severe disease occurs in the countries with greater resource constraints. Therefore the definition of endpoints relevant to LMIC populations and efficacy data from these settings should be planned for in efficacy trials.

Status of vaccine research and development activities
The success of passive immunization with an RSV F mAb (palivizumab and motavizumab) provides the rationale for developing a vaccine that elicits functional antibody responses. While antibodies to F protein are cross-reactive across RSV A and B subtypes, antibodies to G protein are much less so. However, antibodies to the neutralizing site in the central conserved region of G should work on both subtypes, while antibody binding the heavily glycosylated regions of G do not neutralize and would not be cross-reactive. The efficacy of palivizumab and motavizumab, which bind to antigenic site II on the RSV F protein, has led many developers to focus on RSV F as a primary immunogen. As of December 2015, 60 RSV vaccine candidates are in preclinical or clinical development and encompass five broad platforms (Table 1). Live-attenuated approaches targeting pediatric populations have been in development for decades, spearheaded by the US National Institute of Allergy and Infectious Diseases and MedImmune. These were the primary candidates in clinical testing for many years, but recently there has been a significant surge in RSV vaccine candidates using other platforms. While the majority of the vaccine candidates under development are still in the preclinical stage, 16 candidates are now in clinical development. Several of these utilize an RSV F protein-based approach. Novavax, Inc. recently initiated late stage development of both elderly and maternal immunization vaccine candidates (Phase 3), and advanced a pediatric candidate into the clinic (Phase 1). GlaxoSmithKline (GSK, Phase 2), GSK (legacy Novartis, Phase 1), and MedImmune (Phase 2) are also testing RSV F candidates for use in maternal immunization and/or immunization of the elderly. GSK (Phase 1), is testing an adenovirus prime/boost candidate for use in children beyond the neonatal period. Janssen Pharmaceutical (Phase 1) and Bavarian Nordic (Phase 1) advanced to the clinic in 2015 with their own adenovirus and MVA vaccine products respectively. Preclinical vaccine developers include pharmaceutical companies, government agencies, academic institutions, and biotechnology organizations targeting infant, child, and elderly populations (Figure 1).

Recent advances in understanding RSV F protein structure and instability could inform vaccine development.[30] RSV F is present on the viral surface in two states: a metastable pre-F and stable post-fusion (post-F) form. The newly characterized antigenic site Ø has been shown to elicit antibodies more potent than palivizumab in preclinical studies.[31] In addition, there are at least two other sites exclusive to pre-F (AM14 and MPE8) that are more neutralization sensitive than site II.[32] The stabilization of pre-F and its subsequent demonstration of potent immunogenicity has enabled testing of this protein as a vaccine candidate. Several other RSV F protein-based candidates with or without alum adjuvant are currently being developed for maternal immunization. Novavax is advancing a rosetted post-F for their elderly, maternal immunization, and pediatric vaccine candidates. GSK's 2015 acquisition of Novartis Vaccines has united five RSV vaccine candidates using three technologies (pre- and post-F subunit protein, nucleic acid, and gene-based vector) into a single organizational portfolio. MedImmune is advancing a post-F subunit candidate vaccine for the elderly population (Phase 2), and is testing an extended half-life RSV F mAb directed against the newly identified antigenic site Ø to protect infants through their first RSV season. These two enhanced features may make protecting newborns through their first RSV season with a single dose possible, which could provide an alternative to maternal immunization for high-, middle-, and low-income countries.

The success of a maternal immunization strategy will require access to and acceptability of vaccination in pregnant women. Platforms exist for vaccine delivery to pregnant women that leverage the likelihood that, even in the least-developed countries, the majority of women will have some antenatal care.[6] The successful global Maternal and Neonatal Tetanus Elimination Initiative, the recent recommendation by WHO that pregnant women be the highest priority group for influenza vaccine, and the recent recommendation for maternal immunization to protect infants from pertussis by the US Advisory Committee on Immunization Practices all provide important precedents for the acceptance and justification of a maternal immunization approach.

Likelihood for financing
Since the focus of RSV vaccine development in LMICs will be on protecting infants and children younger than five years of age, the vaccines will be in line with the priorities set by Gavi, the Vaccine Alliance. While some RSV burden data are available, additional information is needed to inform evidence-based decisions—particularly mortality, morbidity, and cost of illness data from LMICs. In addition, methods to increase the accuracy of infant mortality data in countries where an appreciable number of home deaths result in underreporting would facilitate case building for RSV vaccines.

Acknowledgements
The authors are grateful to Kathleen Neuzil, John Donnelly, Niranjan Bhat, David Kaslow, and Ruth Karron for their thoughtful review and valuable feedback on this manuscript. This work has been supported by a generous grant from the Bill & Melinda Gates Foundation.

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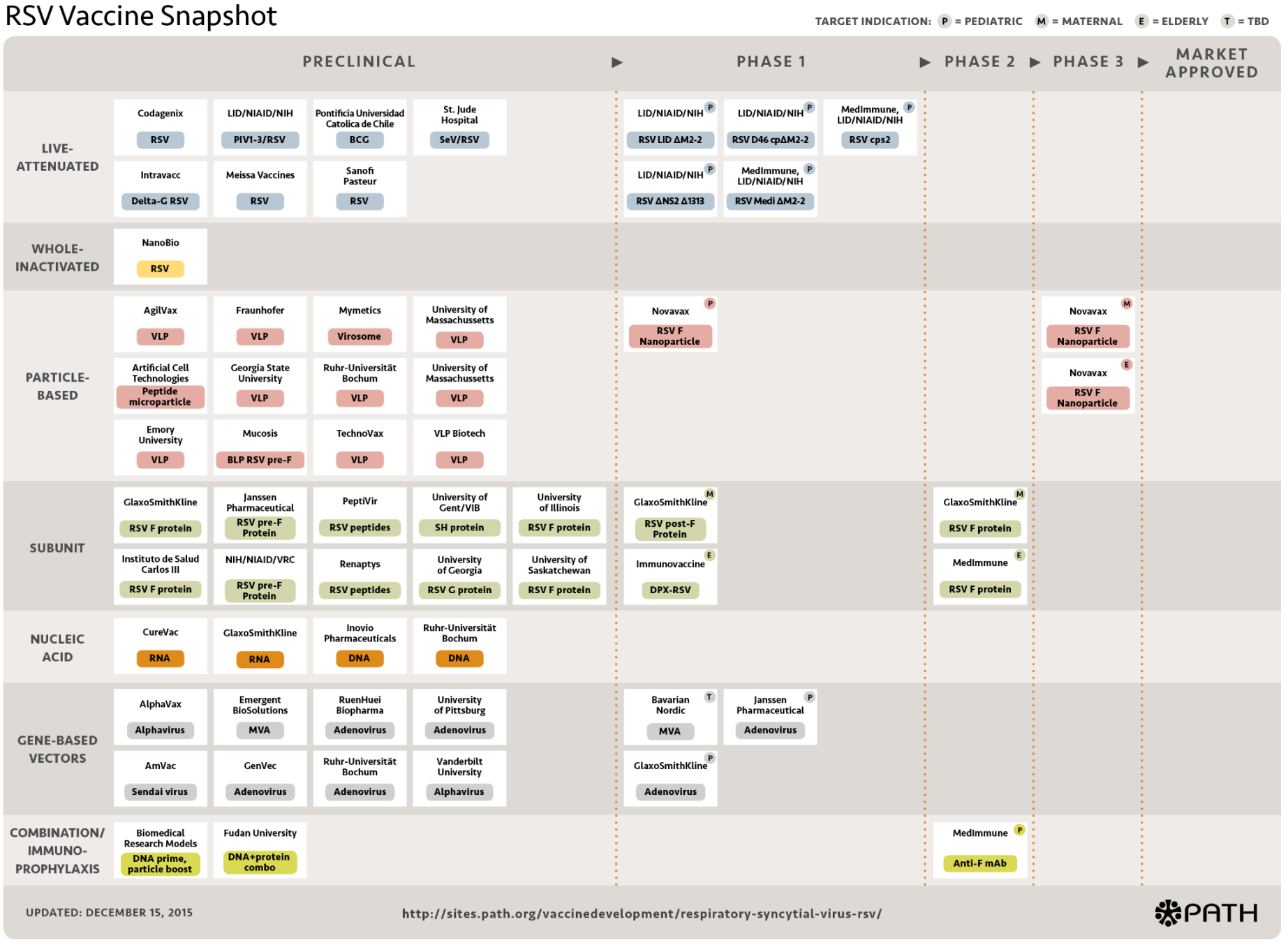
Table 1. RSV vaccine candidate numbers in research and development per vaccine platform.

Vaccine Platform	RSV Vaccine Candidates	
Live-attenuated and live-vectored	12	
Protein-based	30	
• Whole-inactivated		1
• Particle-based		15
• Subunit antigens		14
Nucleic acid	4	
Gene-based vectors	11	
Combination and immunoprophylaxis	3	
	60	**Total**

Figure 1. RSV vaccine candidates in research and development.



Vaccine 34 (2016) 190–197

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

WHO report

WHO consultation on Respiratory Syncytial Virus Vaccine Development Report from a World Health Organization Meeting held on 23–24 March 2015☆

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ARTICLE INFO

Article history:
Received 22 May 2015
Accepted 29 May 2015
Available online 20 June 2015

Keywords:
Respiratory syncytial virus
Vaccine
Clinical development

ABSTRACT

Respiratory syncytial virus (RSV) is a globally prevalent cause of lower respiratory infection in neonates and infants. Despite its disease burden, a safe and effective RSV vaccine has remained elusive. In recent years, improved understanding of RSV biology and innovations in immunogen design has resulted in the advancement of multiple vaccine candidates into the clinical development pipeline. Given the growing number of vaccines in clinical trials, the rapid pace at which they are being tested, and the likelihood that an RSV vaccine will reach the commercial market in the next 5–10 years, consensus and guidance on clinical development pathways and licensure routes are needed now, before large-scale efficacy trials commence. In pursuit of this aim, the World Health Organization convened the first RSV vaccine consultation in 15 years on the 23rd and 24th of March, 2015 in Geneva, Switzerland. The meeting's primary objective was to provide guidance on clinical endpoints and development pathways for vaccine trials with a focus on considerations of low- and middle-income countries. Meeting participants reached consensus on candidate case definitions for RSV disease, considerations for clinical efficacy endpoints, and the clinical development pathway for active and passive immunization trials in maternal and pediatric populations. The strategic focus of this meeting was on the development of high quality, safe and efficacious RSV preventive interventions for global use and included: (1) maternal/passive immunization to prevent RSV disease in infants less than 6 months; (2) pediatric immunization to prevent RSV disease in infants and young children once protection afforded by maternal immunization wanes.

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http://dx.doi.org/10.1016/j.vaccine.2015.05.093
0264-410X/

1. Introduction and objectives

Dr. Vasee Moorthy (WHO) opened the meeting with a description of key processes that lead to licensure, policy recommendation, prequalification and financing of new vaccines for use in low- and middle-income countries (LMICs). The WHO plays an important role in setting up international standards for the quality, safety and efficacy of vaccines, developing policy recommendations, publishing position papers, and assessing priority vaccines for the United Nations Prequalification Program. The Prequalification Program is managed by the WHO and, in close cooperation with national regulatory agencies and partner organizations, aims to make quality vaccines of priority available for the benefit of those in need. Primary considerations for WHO pre-qualification and subsequent investment by the Global Alliance for Vaccines and Immunization (GAVI) include demonstrated efficacy, product quality, safety, implementation feasibility, and affordability [1].

The meeting focused on the clinical development of RSV vaccines for use in LMICs, rather than in high-income countries (HICs), which was scheduled for a separate discussion (notably at the US Food and Drug Administration in June 2015). Topics discussed included: (1) provision of guidance on RSV vaccine clinical development pathways to support evidence-based policy recommendations in LMICs; (2) RSV case definitions and vaccine efficacy endpoints; (3) priority areas and knowledge gaps that need to be addressed for defining a roadmap to RSV vaccine licensure. Additional considerations will also have to be given to the specification of target populations (Table 1) (*i.e.* pregnant women, infants, children), improvement of RSV surveillance and disease burden estimates, and standardization in the choice, methodology, and interpretation of laboratory assays to assess immunogenicity and facilitate prioritization of the vaccine candidate pipeline. With these goals and objectives in mind, there was a program of presentations and guided discussions that involved representatives from academia, industry, and regulatory authorities.

2. Overview of RSV and vaccine development strategies

Dr. Barney Graham (US National Institutes of Health (NIH)) opened with a review of RSV pathogenesis following natural infection and the potential mechanism of disease enhancement observed in the formalin-inactivated RSV (FI-RSV) investigational vaccine trials of the 1960s. The natural history of RSV disease follows from virus tropism for the ciliated epithelia of small bronchioles and type I pneumocytes of the alveoli [2]. The subsequent immune response results in the accumulation of mucus, sloughed epithelium and lymphoid aggregates that obstruct the bronchioles, which partially explains why infants – who have narrower and higher resistance small airways – are more prone to severe bronchiolitis [3]. The mechanism by which the FI-RSV vaccine caused enhanced disease and death, however, differed from the immune responses and pathology associated with natural infection; as the FI-RSV investigational vaccine induced a high titer of binding antibodies relative to the titer of functional inhibiting activity induced, resulting in immune complex deposition and complement activation [4–9]. Additionally, FI-RSV appeared to shift $CD4^+$ T-cell immunity to a Th_2 profile characteristic of allergic inflammation [10,11]. Recent data have demonstrated that the fusion glycoprotein (F) exists in both the native pre-fusion and post-fusion conformations and that virions over time, especially when heated, lose pre-fusion F to an irreversible conformational change to the post-fusion state (*B. Graham, personal communication*). Therefore, the processed virions lose the neutralization-sensitive epitopes present on pre-fusion F and would elicit more post-fusion F-specific antibodies with lower neutralizing potency than observed after natural infection [12,13].

Table 1
Strategic goals for RSV vaccines with a focus on global use.

RSV vaccines for maternal/passive immunization to prevent RSV disease in infants less than 6 months of age
RSV vaccines for pediatric immunization to prevent RSV disease in infants and young children once protection afforded by maternal immunization wanes

The design of an RSV vaccine that is both safe and effective will have to obviate the mechanism by which FI-RSV caused harm in the past. Before embarking on human trials, the immunogenicity and safety of vaccine candidates should be assessed in one or more animal models, including those that exhibit FI-RSV-associated immunopathology. Mice are the most facile model for documenting T cell response patterns following infection or vaccination, manifesting illness and weight loss following high-titer infection, and demonstrating lung pathology consistent with vaccine-enhanced illness seen in children, particularly eosinophilia and alveolitis. Although cotton rats do not exhibit any signs of illness, they are more permissive to infection than mice are (especially neonates) and have more delayed viral clearance. Rats have better standardization than mice for pathologic scoring of alveolitis following FI-RSV immunization and viral challenge [14–16]. The bovine model, though logistically more challenging and expensive to work with, is the most analogous to RSV pathogenesis in humans. The challenge of calves with bovine RSV may cause nearly identical pathology in the bronchiolar epithelium, as is observed following natural infection with human RSV in infants [17]. Although bovine RSV has only partial homology with human RSV, the ectodomain of F is 90% identical and neutralizing antibodies to human RSV F can cross-neutralize bovine RSV, allowing indirect testing of human vaccines. Given the safety concerns of previous vaccine candidates, evaluation of RSV vaccine candidates intended for use in antigen-naïve infants will need to be performed in animal models to support a rationale for why the vaccine approach would have an acceptable safety profile in this population.

Dr. Ruth Karron (Johns Hopkins University) reviewed promising vaccine candidates entering, or already in, clinical trials. These include more than ten candidates delivered as protein subunits, live-attenuated viruses, or recombinant viral vectors (Fig. 1). The primary goal of RSV vaccination is protection against RSV lower respiratory tract illness (LRTI) in the target population, as induction of sterilizing immunity is unlikely to occur. As infants are the priority population for both active and passive immunization, consideration must be given to how maternal factors may influence vaccine efficacy. These factors include the phenomena of infant immune response suppression by maternal antibody and transplacental antibody transfer in the setting of HIV infection, hypergammaglobulinemia, or placental malaria [18,19]. Developers and regulators will also have to decide whether the guidance used for the past few decades still applies: that only live-attenuated viruses be used in pediatric populations and subunits or other non-replicating vaccines are best used for maternal immunization.

Dr. Peter Collins (NIH) provided additional details on the live-attenuated and live-vectored RSV vaccines currently in clinical development. Live vaccines have the advantage of inducing broad humoral and cellular immunity without requiring an adjuvant and are not likely to cause FI-RSV enhanced disease, as they present viral surface glycoproteins in their native conformations [20,21]. However, because these live viruses induce immunity through replication, they must be highly attenuated [22]. Dr. Collins presented vaccines based on three live attenuated RSV strains, two of which have recently completed phase I clinical trials in RSV seronegative infants. Surveillance data following administration of one candidate suggests that immunization primes for an anamnestic RSV neutralizing antibody response. More than one

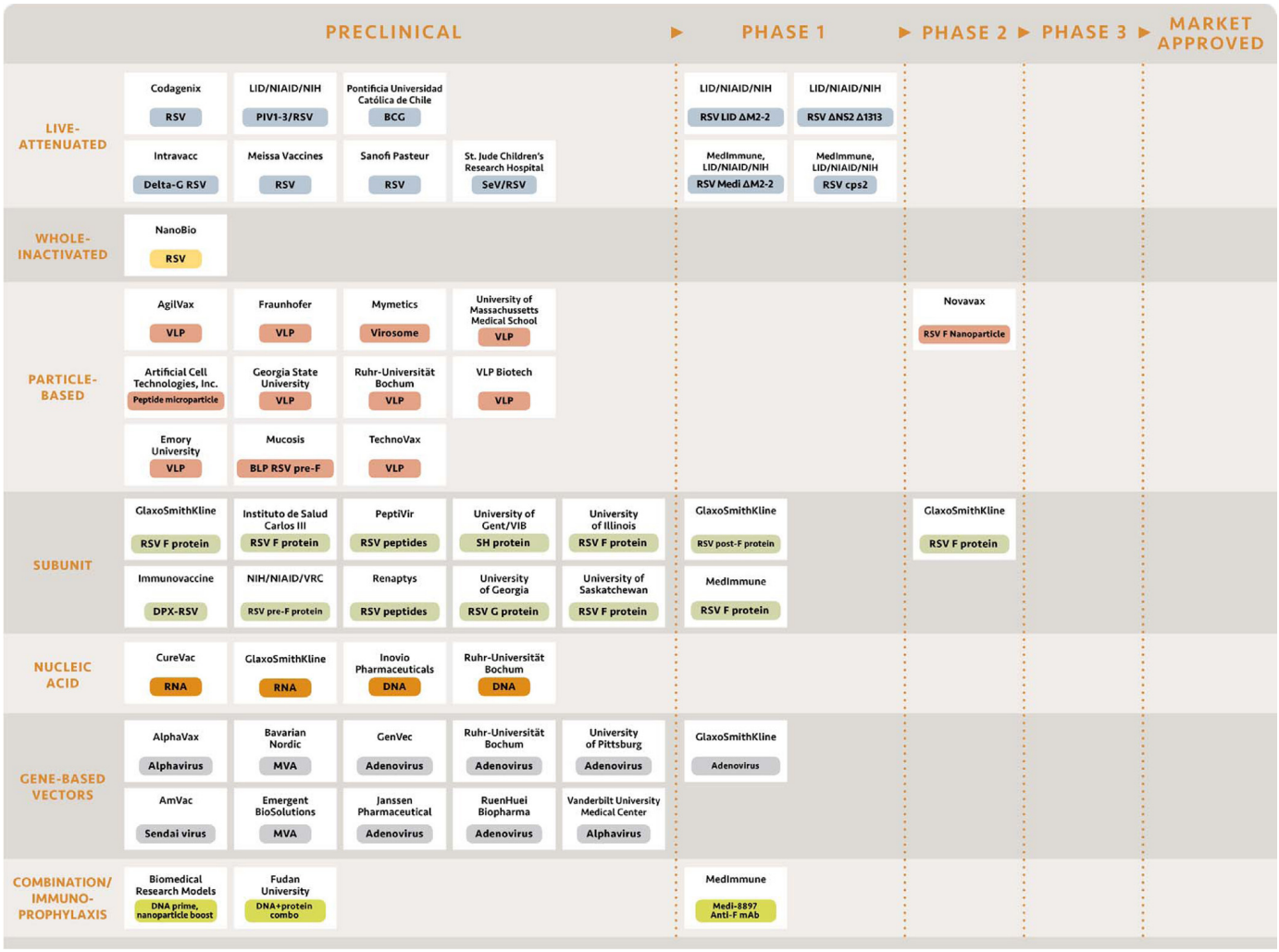

Fig. 1. RSV vaccine candidates in pre-clinical and clinical development (adapted from PATH RSV Vaccine Snapshot).

live-attenuated vaccine candidate is likely to be advanced further for clinical testing in larger and more diverse populations.

3. RSV epidemiology: Burden estimates and knowledge gaps

Drs. Janet Englund (University of Washington), Harish Nair (Centre for Population Health Sciences, University of Edinburgh) and James Nokes (KEMRI Wellcome Trust/Warwick University) each presented on the progress and challenges in measuring RSV incidence, disease burden, and mortality in LMICs. One complicating factor is the variation in seasonality of disease burden within and across global regions. While mid-winter epidemics tend to occur in temperate zones, seasonality is less pronounced and occasionally absent in tropical and arctic climates [23–25]. These findings come with the caveat that data from LMICs, particularly in infants less than six months old, are sparse [26] and may require special considerations for additional factors such as low birth weight and ambient air quality. Increasing amounts of RSV hospitalization data are becoming available through influenza surveillance activities, though case definitions may need to be modified to have sufficient sensitivity for detection of RSV cases, particularly in young infants. Incidence rates vary widely across studies due to differences in diagnostic methods, viral subtype, and co-infection prevalence. In addition, there are wide variations in the duration of hospitalization among infants with RSV in different socio-economic settings [27–29].

In 2010, there were an estimated 33 million global cases of RSV-associated LRTI [26]. Although, this estimate was based on community-based studies with active data, it was only from 24 data points. Revised incidence estimates of severe RSV ALRI, based on 73 data points, are currently being calculated (*Harish Nair, personal communication*). Dr. Nokes presented data from one community-based cohort study in Kilifi, Kenya [28,30], which used active surveillance and set criteria for hospital referral as high respiratory rate for age, as assessed by field workers during weekly home visits. The incidence rate of RSV-associated LRTI was six-fold higher when measured by active, compared to passive, surveillance [28].

These findings suggest the incidence or duration of hospitalization due to RSV, used as a primary endpoint in RSV vaccine trials and/or as a surrogate measure of severe disease would be highly variable between settings for reasons unrelated to RSV epidemiology. Furthermore, because many cases of RSV disease do not present to the hospital, there was general consensus on a need for studies involving increased active surveillance or facilitated passive surveillance, linked to community-based data collection, to better inform trial design in LMICs. In addition, background rates of potential adverse events need to be characterized in areas where clinical trials of maternal vaccination are planned for intrauterine fetal demise, congenital malformation,

prematurity and intrauterine growth retardation. For trials of live attenuated pediatric vaccines, wheezing in infants should also be monitored. Preparation for pivotal vaccine trials will require a preparatory phase of data collection through longitudinal, epidemiological studies with standardized case ascertainment. This will better inform trial design and result in more robust sample size estimates.

4. RSV vaccines in advanced clinical development

Representatives from industry presented the profiles of their most advanced RSV vaccine candidates and discussed target populations, clinical endpoints, trial designs, and safety measures. Dr. Allison August (Novavax) outlined the characteristics of the rosetted post-fusion subunit vaccine that has been shown, in phase II trials, to elicit antibodies that inhibit Palivizumab binding in non-pregnant women of child-bearing age [31,32]. A phase II study to assess safety and immunogenicity in pregnant women is underway and a phase III trial of this vaccine candidate in pregnant women is planned to start in the final quarter of 2015. In this trial, women will be administered a single dose of the vaccine during the third trimester of pregnancy, and their infants will be evaluated for incidence of RSV-associated LRTI with hypoxemia (the decision is still to be made on the oxygen saturation (SpO_2) threshold) through the first six months of life. The minimal criteria for efficacy and duration of protection were stated to be 60% and 3 months, respectively.

Dr. Filip Dubovsky (MedImmune) described the company's live-attenuated and live-vectored RSV vaccine program and gave an update on the development [33–35] of their extended half-life monoclonal antibody (MEDI8897), directed at the recently characterized antigenic site Ø on pre-fusion F [12,13]. The live-attenuated vaccines demonstrated shedding, generated a moderate level of antibody responses, and were not associated with enhanced disease. However, increased rates of LRTI that were observed among some vaccinees will require additional evaluation to understand if this finding represents a true safety signal. As for prior vaccine candidates, the efficacy trial endpoints for MEDI8897 will include RSV-associated LRTI.

Although at an earlier stage of clinical development, passive prophylaxis with the next-generation monoclonal MEDI8897 appears significantly superior to Palivizumab (a licensed monoclonal antibody for the reduction of serious LRTI caused by RSV infection in high risk infants), with a 9-fold increase in *in vivo* potency and an extended half-life that could offer protection for several months following a single fixed-dose intramuscular administration. Given this potential for greater efficacy, and planned tiered-pricing of the product, a single birth dose of MEDI8897 may ultimately prove cost-effective for protection of infants in LMICs. However, the pathway to prequalification for such a product would need to be created *de novo*, as no monoclonal antibodies are currently prequalified by the WHO.

Dr. Ilse Dieussaert (GlaxoSmithKline Biologicals) described two parallel vaccine development pipelines for maternal and pediatric populations. Phase I data on an adjuvanted recombinant protein subunit intended for maternal vaccination showed no safety signals and moderate immunogenicity with higher neutralizing responses than previous post-fusion F vaccine antigens. As phase III trials are envisioned, particular attention is being given to defining the most reliable and relevant efficacy endpoints for different settings and age groups. Dr. Dieussaert provided a list of signs and symptoms for defining LRTI and severe LRTI that are currently being evaluated in large-scale epidemiologic studies in both high and low resource settings. Although each of the industry representatives proposed a list of possible endpoints for vaccine trials, there was general agreement that RSV-associated LRTI and severe LRTI, however they are to be defined, would be better primary outcome measures than hospitalization (or death).

5. Regulatory considerations

Regulators from the US (Dr. Jeff Roberts, FDA Center for Biologics Evaluation and Research), UK (Dr. Mair Powell, Medicine and Healthcare Products Registry), South Africa (Dr. James Southern), and Ghana (Mr. Eric Karikari-Boateng) offered their perspectives on the routes to RSV vaccine licensure. There was general agreement that clinical efficacy studies can feasibly be performed for RSV vaccines and would be required for licensure. In addition to reviewing the quality, safety and efficacy of the submitted product, regulatory authorities will also have to consider specific RSV-related issues. These include the necessity for increased vigilance for vaccine enhanced disease in neonates and antigen-naïve infants, development of a safety database for a first-in-class vaccine to prevent disease in infants through vaccination of pregnant women, and possible use of different vaccine platforms for immunization of pregnant women and young children for the same disease.

In phase III trials, regulatory agencies expect efficacy endpoints to reflect clinically relevant disease prevention, with verification of cases through both laboratory and clinical parameters. Although the minimum number of vaccinees in pre-licensure studies for an adequate safety database is not always prescribed, the numbers required for approval of recently licensed novel vaccines have varied from about 6000 to over 40,000 (the latter in the case of rotavirus vaccines, where theoretical safety signals drove the sample size) [36,37]. The prerequisites for a successful licensure or marketing authorization approval will be addressed on a case-by-case basis in discussion with the manufacturer.

6. Duration of follow-up

It was preferred that actively immunized infants should be tracked through two RSV seasons to provide evidence of efficacy, cross-protection against multiple viral strains, and durability of response. While vaccine efficacy is expected to persist for 6 months or less after passive immunization, extended follow-up could be relevant for detection of unexpected adverse events in children who were protected against severe RSV infection during their first season but experienced RSV infection during the second year of life. Deferral of disease may still provide substantial clinical benefit, as older infants are likely to be better able to mount a robust immune response and recover more quickly, with likely lower mortality and fewer long-term sequelae [38,39]. However, it is recommended that the frequency and severity of illness and pattern of immune responses to infection be monitored during the next season. Extended follow up may be considered in the post-marketing surveillance periods, with a specific focus on the impact of immunization on long term wheezing.

7. Geographical settings for clinical trials

Clinical efficacy trials of RSV vaccine candidates are likely to be conducted in both HICs and LMICs. Regulators from LMICs emphasized the need for efficacy data relevant to low-resource settings and the importance of defining endpoints relevant to target populations. The oft-used endpoint in HICs of medically attended RSV disease may be less relevant in LMICs. For example, in some settings a significant proportion of children with acute respiratory symptoms may not seek medical care or may make their first clinical contact with a non-medical provider [40]. The choice of primary endpoints in clinical trials will have to take account of the cultural context in which the trials are being conducted. However, it will be

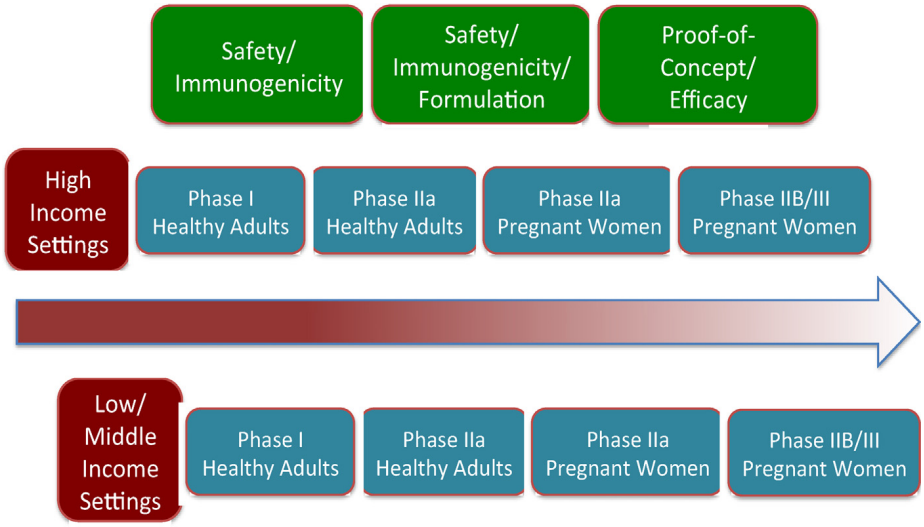

Fig. 2. RSV vaccine clinical development pathway for pregnant women.

desirable to construct widely applicable endpoints with objective clinical criteria to define severe and very severe LRTI, and highly specific validated PCR assays to confirm RSV infection. Collaborations between Northern and Southern hemisphere clinical trials sites and harmonization of clinical endpoints will accelerate the evaluation of vaccines because of the complementary seasonality of RSV infection.

8. Clinical development pathway for maternal immunization

As a precaution and a legacy from the experiences of FI-RSV enhanced disease, phase I trials that involve antigen-naïve infants, in any age group or population, should occur in a setting with good facilities for the management of adverse events. These facilities should have the capacity for vigilant follow-up throughout the RSV season and the availability of and access to ventilatory support. For example, the first trials could be conducted in HICs in North America, Europe or Australia followed by trials in lower resource settings. Thus, a staggered development pathway would allow for the procession of trials in lower income settings soon after safety data emerge from higher resource settings.

There was general agreement among meeting participants on the pathway to develop and license an RSV vaccine that would prevent RSV disease in infants less than 6 months of age through maternal immunization (Fig. 2). Novel vaccine candidates that meet preclinical criteria for use in human trials should first be tested in trials that assess safety and immunogenicity in healthy adults, including non-pregnant women. Once data become available from these trials, the dose, schedule and administration route can then be selected from trials in healthy women in their third trimester of pregnancy. Additionally, data will need to be collected on prematurity, intrauterine fetal demise, and other serious adverse perinatal outcomes. A single dose vaccine is desirable, as multiple doses might be associated with decreased uptake. In any trial of pregnant women, both mother and infant should be followed for at least 6 months post-delivery, and preferably for longer into the second RSV season.

One or more preliminary trials in pregnant women may provide sufficient data to demonstrate transfer of functional maternal antibody to the infant, persistence of maternal antibody, and overall reduction of RSV disease in infants, but will not be powered to provide definitive estimates of vaccine efficacy. These preliminary studies will therefore be used to inform the design of one or more larger, confirmatory vaccine efficacy trials. It is also possible that once the dose, schedule and administration route have been selected, preliminary and confirmatory vaccine efficacy data could be obtained from the same trial based on predetermined protocol-specified criteria, *e.g.* by incorporating an event-driven interim analysis. These trials could also evaluate more than one regimen – in the event of continued uncertainty regarding the optimal dose or schedule – by using an adaptive trial design. In this case, emphasis will be placed on the statistical procedures that govern such an adaptive design.

Determination of vaccine efficacy should be based on follow-up of infants for at least 6 months or for as long as maternal antibody has been documented to persist. Trials may need to be carefully timed such that the maternal vaccination period will result in births coinciding with the early part of the RSV season. The follow up in infants for safety is expected to be at least 12 months from delivery, and at least 12 months from vaccination for safety in the mother, and likely longer into the second RSV season. If timed appropriately, it may be possible to conduct more than one confirmatory vaccine efficacy trial across multiple geographical settings. If low and high income settings are merged into a single trial, thought should be given to the design and implementation of case definitions, case detection systems, endpoints, and study procedures that are applicable to all trial settings. Furthermore, the estimated distribution of cases contributing to key endpoints and differing cultural contexts and community engagement procedures must be well understood for each setting prior to trial initiation.

In general, the regulatory approach to the question of benefit (or lack thereof) in pregnant women may be driven by the desired indication sought by the manufacturer. If there is no claim of benefit to pregnant women, then there may be no requirement to demonstrate benefit. For example, the language "prevention of RSV disease in infants through vaccination of pregnant women" does not imply any direct benefit to the mother. However, sponsors are encouraged to collect data on RSV incidence in vaccinated and unvaccinated mothers as is feasible. Co-administration of vaccines is likely to be an important issue as well, particularly in LMICs where fewer antenatal visits mean fewer opportunities to vaccinate pregnant women. In LMICs, tetanus vaccine is likely to be co-administered with a licensed RSV vaccine, while TDaP and influenza vaccines are more likely to be co-administered in HICs.

Table 2
WHO candidate case definitions for severe and very severe RSV associated lower respiratory tract infection (LRTI).

Severe RSV LRTI	Very severe RSV LRTI
An infant or young child presenting to a health facility that is part of the case ascertainment system for the phase III trial who fulfills both the laboratory AND clinical criteria below: **Laboratory criterion** RSV infection as confirmed by a fit-for-purpose, fully validated PCR assay with high specificity and sufficient sensitivity on upper respiratory samples **Clinical criteria** Respiratory infection defined as cough or difficulty breathing AND LRTI defined as fast breathing by WHO criteria or SpO_2 < 95% AND ≥1 of the following features of severe disease – Pulse oximetry < 93% – Lower chest wall in-drawing	An infant or young child presenting to a health facility that is part of the case ascertainment system for the phase III trial who fulfills both the laboratory AND clinical criteria below: **Laboratory criterion** RSV infection as confirmed by a fit-for-purpose, fully validated PCR assay with high specificity and sufficient sensitivity on upper respiratory samples **Clinical criteria** Respiratory infection defined as cough or difficulty breathing AND LRTI defined as fast breathing by WHO criteria OR SpO_2 < 95% AND ≥1 of the following features of very severe disease – Pulse oximetry < 90% – Inability to feed – Failure to respond/unconscious

9. Clinical development pathway for pediatric immunization

The approaches to the development of pediatric RSV vaccines are more diverse than those to maternal RSV immunization. For this reason, there was no consensus among meeting participants on a specific framework for this target population. However, meeting participants generally agreed on an initial requirement for studies of safety and immunogenicity in healthy adults. Safety data would be expected from RSV-seropositive subjects before progressing to the target population of seronegative infants. Additionally, it would also be necessary to assess safety and immunogenicity during co-administration with representative routine vaccines administered to target age groups.

10. Clinical case definitions for RSV vaccine efficacy trials

Meeting participants agreed that re-analyses of existing epidemiological data and initiation of new epidemiological studies will better inform the design of RSV vaccine trials. After considering case definitions proposed by different groups and ongoing work to update the WHO pneumonia clinical management guidelines, consensus was achieved on candidate case definitions for severe and very severe RSV-associated LRTI (Table 2). The case definitions included clinical features considered to be objective, easily standardized, generalizable across settings, and generally accepted markers of severe or very severe RSV disease. Of note, these case definitions rely heavily upon pulse oximetry. Thus, emphasis was placed on the importance of using appropriate instruments and standardized methods for obtaining pulse oximetry readings. It was proposed that these definitions be piloted in ongoing epidemiologic and surveillance studies, as well as in vaccine efficacy trials. The epidemiological studies could provide valuable information across settings on the sample size needed to demonstrate an effect against severe and very severe RSV-associated LRTI.

11. Access for LMIC populations

For vaccine manufacturers the major economic market for RSV vaccines is likely to be in HICs. Post-trial availability of the vaccine in LMICs should be a requirement before RSV vaccine trials are conducted. Stakeholders will have to ask and address the question of when and how is it appropriate to test vaccines in LMICs and what assurances should be in place before such trials occur. In the case of malaria vaccines, it was deemed helpful to include a "neutral party" who would not stand to gain financially if the vaccine was licensed. A product development partnership fulfilled this role for a multi-site African phase III malaria vaccine trial. These are important questions that were not fully addressed at this meeting and merit further evaluation as the RSV vaccine field progresses.

The principle of global access to a safe and effective vaccine has been a well-established principle of previous WHO consultations. Specifically, the WHO will not condone a scenario where a vaccine has been found to be safe and effective partly through testing in LMIC settings but only becomes available in high-income markets. Through the principle of equity, access to vaccines should be based on public health need and not population income. Given that RSV disease burden is disproportionately shifted toward LMICs, there is a major onus on developers/funders to work towards ensuring access, availability and affordability in these settings early in the development and testing cycle.

12. Development of reference reagents for RSV vaccines

The majority of RSV vaccine development strategies aim to elicit RSV-specific functional antibodies, as they have long been associated with protection from RSV disease. There are nearly a dozen different assays in use that measure virus neutralizing antibodies, making it difficult to directly compare immunogenicity data across different vaccine candidates. Plaque reduction neutralization (PRNT) is considered the gold standard, but it is a manual, labor-intensive, and lengthy process not easily standardized across laboratories. Microneutralization assays offer some improvement in efficiency through higher throughput detection of viral infectivity. The addition of complement or the use of reporter viruses can also increase assay sensitivity. Still, there is little consensus within the RSV field on what assays, and, more specifically, which method to use and how to report results. Dr. Deborah Higgins (PATH) described an effort by PATH, WHO, and the National Institute for Biological Standards and Control to harmonize data across various formats through the development of a series of clinical assay reference reagents – available to product developers – to facilitate evaluation and enable prioritization of early stage vaccine candidates. The longer-term goal of this activity is to establish one or more of these reagents as International Standards that are applicable to a broad range of assays, enabling comparison of data across studies, regardless of specific assay methodology.

Table 3
List of consultation participants.

Name	Organization	Location
Participants		
Narendra Kumar Arora	The INCLEN Trust International	New Delhi, India
Louis Bont	University Medical Center, Utrecht	Utrecht, The Netherlands
Harry Campbell	Centre for Global Health Research	Edinburgh, UK
Peter Collins	National Institutes of Health	Bethesda, MD
Janet Englund	University of Washington	Seattle, WA
Barney S. Graham	National Institutes of Health	Bethesda, MD
Eric Karikari-Boateng	Food and Drugs Authority	Accra, Ghana
Ruth Karron	Johns Hopkins Bloomberg School of Public Health	Baltimore, MD
David Kaslow	PATH	Seattle, WA
Shabir A. Madhi	National Institute for Communicable Diseases	Johannesburg, South Africa
Harish Nair	Centre for Global Health Research	Edinburgh, UK
Patricia Njuguna	KEMRI Wellcome Trust	Kilifi, Kenya
James Nokes	KEMRI Wellcome Trust; Warwick University	Kilifi, Kenya; Coventry, UK
Fernando Polack	Fundación INFANT	Buenos Aires, Argentina
Mair Powell	Medicines and Healthcare Products Regulatory Agency	London, UK
Nienke Scheltema	Wilhelmina Children's Hospital	Utrecht, Netherlands
Claire-Anne Siegrist	Centre Médical Universitaire	Geneva, Switzerland
Eric A.F. Simoes	University of Colorado Health Sciences Center	Denver, CO
Peter Smith	London School of Hygiene and Tropical Medicine	London, UK
James Southern	Medicines Control Council	Simon's Town, South Africa
Observers		
Allison August	Novavax Inc.	Gaithersburg, MD
Ilse Dieussaert	GlaxoSmithKline Biologicals	Wavre, Belgium
Filip Dubovsky	MedImmune	Gaithersburg, MD
Amy Fix	Novavax Inc.	Gaithersburg, MD
Jorge Flores	PATH	Seattle, WA
Gregory Glenn	Novavax Inc.	Gaithersburg, MD
Pamela Griffin	MedImmune	Gaithersburg, MD
Deborah Higgins	PATH	Seattle, WA
Keith Paul Klugman	The Bill & Melinda Gates Foundation	Seattle, WA
Jean-François Toussaint	GlaxoSmithKline Biologicals	Wavre, Belgium
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WHO Secretariat		
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Terry Gail Besselaar	HIP/HSE, WHO-HQ	Geneva, Switzerland
Brigitte Giersing	FWC/IVB, WHO-HQ	Geneva, Switzerland
Ivana Knezevic	HIS/EMP, WHO HQ	Geneva, Switzerland
Kayvon Modjarrad	FWC/IVB, WHO HQ	Geneva, Switzerland
Vasee Moorthy	FWC/IVB, WHO HQ	Geneva, Switzerland
Wenqing Zhang	HIP/HSE, WHO-HQ	Geneva, Switzerland
Tiequn Zhou	HIS/EMP, WHO-HQ	Geneva, Switzerland

13. The concept of an RSV vaccine roadmap

Dr. David Kaslow (PATH) outlined the critical role of the malaria vaccine technology roadmap in prioritizing activities for research, product development, capacity building, policy and commercialization for the purpose of achieving licensure, recommendation and uptake of malaria vaccines. This process has been and continues to be instrumental in establishing a shared vision and strategic goals through consultation with multiple stakeholders, and is reviewed every 5 years or sooner if new data become available that change strategic thinking. The WHO proposed that a similar process be established to identify gaps in the product development pathway for RSV vaccines, to meet the two agreed strategic goals, namely a vaccine for maternal/passive immunization to prevent RSV disease in those under 6 months, and a vaccine for pediatric immunization to prevent RSV disease in infants and young children. This will be drafted through consultation of an RSV Roadmap Working Group, will provide guidance rather than a prescription of the way forward, and is anticipated to be available by mid-2016.

14. Conclusions

There are about ten RSV vaccine candidates currently in clinical trials and several dozen in pre-clinical development (Fig. 2). After several decades of addressing major challenges in vaccine design and development, the RSV vaccine field is poised to enter a new phase involving late stage testing of more than one vaccine approach. As RSV disease burden and mortality disproportionately affect infants and young children living in LMICs, actions need to be taken now to ensure pivotal phase III efficacy trials include key populations and endpoints that are relevant to developing countries. An initial step toward clinical development of RSV vaccines for global use was achieved through this WHO consultation. Representatives from higher and lower income countries (Table 3) convened and agreed upon two target populations for vaccine testing and use (pregnant women and young children), the general principles of a clinical development pathway for these two populations (Fig. 2), and candidate case definitions for severe and very severe RSV disease (Table 2).

As more vaccine candidates enter clinical development and efficacy trials, it will be the task of regulators, researchers, manufacturers, and governmental bodies to further refine the agreements and definitions that were discussed at this meeting and to develop population-specific information to optimize vaccine safety, efficacy, and implementation feasibility. To provide guidance toward those ends, the WHO is creating working groups to develop a preferred product characteristics document (to guide target product profiles) and a vaccine roadmap. These guides will offer a more detailed vision of the path forward for an RSV vaccine that is intended for global use.

Acknowledgements

We acknowledge the preparatory analysis of endpoints and case definitions used in previous RSV preventive intervention trials developed by Prof. Eric Simoes of the University of Colorado Health Sciences Center, Denver, Colorado, USA. Fig. 1 is adapted from the PATH RSV Vaccine Snapshot. We acknowledge the technical input into the preparation for the consultation by the following individuals: Professor Barney Graham of Vaccine Research Center, NIAID, Bethesda, MD, USA; Professor Ruth Karron of Center for Immunization Research, Johns Hopkins University, Baltimore, MD, USA and Dr Jeff Roberts, US Food and Drug Administration, Center for Biologics Evaluation and Research, Silver Spring, MD, USA. WHO's RSV vaccine acitivities are guided by a Technical Advisory Group consisting of Prof. Narendra Arora, the INCLEN Trust International, New Delhi, India; Dr Mair Powell, Medicines and Healthcare Products Regulatory Agency, London, UK; Prof. Helen Rees, Wits Reproductive Health and HIV Institute, Johannesburg, South Africa and Prof. Peter Smith, London School of Hygiene and Tropical Medicine, London, UK. We gratefully acknowledge funding from the Bill & Melinda Gates Foundation to support the consultation reported here.

The views, findings, and conclusions contained within are those of the authors and should not be construed to represent the positions or policies of the Bill & Melinda Gates Foundation, the US Department of Defense or the World Health Organization.

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19-20 January 2015

11th Meeting of the SAGE Polio Working Group

Conclusions and recommendations

Note for the Record

World Health Organization

DRAFT AS OF 3/8/16

Background

The 11th face-to-face meeting of the SAGE Polio Working Group (WG) was held during 19-20 January 2016 at the World Health Organization in Geneva, Switzerland.

The meeting was attended by the following WG members: Yagob Al-Mazrou (Chair), Peter Figueroa (Ex-chair), Elizabeth Miller (Ex-chair), Francis Nkrumah, Walter Orenstein, Antoine Kabore, Kimberly Thompson, Nicholas Grassly, Walter Dowdle, Hyam Bashour, T Jacob John and Zulfiqar Bhutta.

This note presents a summary of the main findings, conclusions and recommendations of the meeting.

Context and objectives of the Meeting

In October 2015, SAGE reaffirmed that the withdrawal of type 2 oral polio vaccine (OPV type 2) should proceed in April 2016, through a globally synchronized switch from trivalent to bivalent OPV (the tOPV-bOPV switch). This decision was based on an assessment that the public health risks associated with continued use of the type 2 component of trivalent oral polio vaccine (tOPV) outweigh the risks associated with withdrawing this component of the vaccine. SAGE also recommended risk mitigation measures, including implementing an aggressive schedule of Supplementary Immunization Activities (SIAs) with tOPV, strengthening response to outbreaks in Guinea and South Sudan, accelerating implementation of WHO Global Action Plan for containment (GAPIII), and prioritizing an adequate IPV supply to countries at higher risk of type 2 polio outbreaks.

The WG met on 19-20 January 2016 to: Follow up on the SAGE recommendations regarding OPV type 2 withdrawal; and ii) start discussions on future immunization policy after OPV type 2 withdrawal. The specific objectives of the meeting were:

1. To appraise the current epidemiology of cVDPV2
2. To examine the status of preparation for OPV type 2 withdrawal
3. To discuss the roadmap for SAGE discussions and recommendations on future polio immunization policy
4. To review the epidemiology of immunodeficiency-related vaccine-derived polioviruses (iVDPVs), progress on antiviral agents, and options for increasing sensitivity of surveillance for iVDPV.

Topic 1: Current cVDPV epidemiology

The WG reviewed progress towards interruption of wild poliovirus (WPV) and type 2 circulating Vaccine-Derived Poliovirus (cVDPV2). In the last six months, WPV cases have only occurred in Pakistan and Afghanistan, with no cases in the Middle East (last case 7 April 2014) or Africa (last case 11 Aug 2014). The number of WPV1 cases declined in both Pakistan (from 306 in 2014 to 52 in 2015) and Afghanistan (from 28 to 19 respectively). No WPV3 has been detected globally for over three years.

In Afghanistan, two epidemiological blocks can be distinguished: the Southern Region (Helmand and Kandahar) and the Eastern Region (Nangarhar and Kunar). Security issues continue to limit access, particularly in the Eastern Region. Repeated cross-border transmission with Pakistan is affecting the Eastern Region. The program has designated 47 high-risk districts in which efforts to address access and campaign quality issues are being focused, and plans to conduct targeted SIAs combining both OPV and Inactivated Polio Vaccine (IPV) in 28 highest-risk districts.

In Pakistan, the number of children in inaccessible areas has been reduced from more than 600,000 in 2013 to 16,000 in 2015. The programme is prioritizing efforts to access the remaining unreached children, and maximizing immunity through a series of strategies including OPV SIAs, using IPV in specific areas, setting-up health camps, and expanding Continuous Community Protected Vaccination[1] (CCPV).

[1] In CCPV, full-time volunteers are appointed from local areas and they work throughout the month. These volunteers are typically assigned the task to cover small areas.

The program has also made progress in eliminating persistent cVDPV2. There have been no persistent cVDPVs since March 2015 in Pakistan and since May 2015 in Nigeria. However, there have been several VDPV emergences in 2015, including cVDPV2 outbreaks in Guinea and Myanmar, and cVDPV1 outbreaks in Ukraine, Laos and Madagascar. The program has launched extensive response activities to these outbreaks. The response in Guinea has faced challenges, including suboptimal quality of SIA campaigns, and needs to be further intensified to ensure that the outbreak is stopped before the tOPV-bOPV switch. Surveillance for poliovirus remains in abeyance in Liberia and Sierra Leone, the other two Ebola-affected countries adjacent to Guinea.

WG decisions/recommendations

- **WPV**: The WG noted the significant progress made in improving access and coverage, and decreasing the number of type 1 WPV cases in Pakistan and Afghanistan. The WG encouraged the program to further accelerate progress, especially in improving the monitoring of SIAs, strengthening surveillance and improving access in key areas (particularly Karachi, Peshawar, Khyber in Pakistan and the Eastern Region of Afghanistan), and reaching missed children including by addressing socio-cultural barriers.
- **VDPV2**: The WG acknowledged the progress made in eliminating persistent cVDPV2 in Pakistan and Nigeria (i.e. no case since May 2015), however the WG expressed its continuing concern about Pakistan. The WG judged that the response to the VDPV outbreak in Myanmar is adequate. However, the WG was concerned about the outbreak response in Guinea. The WG recommends that the program should further intensify the response to this outbreak. The WG also recommends that the program intensify programme surveillance (including expedited shipment of AFP samples, and establishment of environmental surveillance sites) in Guinea and its neighbouring and recently Ebola-affected countries of Sierra Leone and Liberia.
- **Rapid detection of VDPV2:** The WG recommends that the Global Polio Laboratory Network (GPLN) should continue to optimize diagnostic methods to rapidly detect poliovirus in AFP and environmental samples. Moreover, the GPLN, needs to be able to provide additional programmatically relevant information on any isolated type 2 polioviruses (i.e... whole genome sequencing and determination of recombination with class C enteroviruses) in an accelerated manner, to allow timely institution of appropriate response measures, particularly after the tOPV-bOPV switch.

Topic 2: Review the status of preparation for OPVOPV type 2 withdrawal

Type 2 cVDPV outbreak risk and response protocol

The WG reviewed a summary of a discussion held (on 18 January 2016) between representatives of the WG (Al-Mazrou, Figueroa, Grassly, Orenstein, Thompson) and three modelling groups (Kid Risk, Institute for Disease Modelling and Imperial College London) on cVDPV2 emergence risks and response strategy (see appendix 1). The WG also reviewed the updated type 2 outbreak protocol that had been revised since the September WG's previous meeting (see appendix 1).

Key changes made to the protocol since that time, in response to extensive internal and external review were:1) adjustments to the scenarios in which IPV will be used; 2) adjusting the response activities for VDPVs, WPVs, and Sabin poliovirus by geographic zones; and 3) expanding the use of mOPV2 in response to a WPV2 AFP case or detection in environmental sampling (ES). The protocol emphasizes the primacy of rapid institution of control measures (an mOPV2 SIA within two weeks), recognizing that coverage of the initial rapid response may not be optimal. Even with sub-optimal coverage, mathematical models project substantial impact on reducing transmission, if done quickly and followed up by high-quality subsequent rounds. WHO Country Offices and UNICEF Supply Division have confirmed that deployment of mOPV2 within 2 weeks and IPV within 30 days after the decision of WHO DG to release stockpile is feasible, if adequate supplies of IPV are available.

There is a continuing IPV shortage globally, which will likely persist into 2017. For this reason, intradermal (ID) fractional-dose IPV should be used for outbreak response, preferably administered with an ID device rather than a needle and syringe. It is anticipated that the first ID IPV device will become available in June 2016, and the next in October/November 2016. There is an ongoing study in Pakistan to assess the immunogenicity (i.e. humoral immunity) of ID IPV and its usability in SIAs, with a similar study planned in the African region. Administering IPV in previously OPV-vaccinated children is boosting of mucosal immunity and providing

protection from paralysis for serotypes for which the IPV leads to seroconversion, which will contribute to decreasing the burden of poliovirus associated with the outbreak.

WG decisions/recommendations

- Based on the mathematical models considered, the program should expect at least 1-2 cVDPV type 2 outbreaks within the first 12 months following the switch, with Pakistan representing a high-risk area.
- It is important to fully sequence any newly detected type 2 VDPV strain rapidly, to identify whether or not an outbreak response is required iVDPV requiring a different set of response activities.
- The WG endorsed the revised protocol, including:
    - The use of IPV in the case of "confirmed" outbreaks in Zone 1-2 countries.
    - Minimum number of SIAs (4 or more SIAs)
    - Target age group (0-5 years unless epidemiology suggests older persons involved)
    - Minimum target population (2 million)
- Recognizing the continuing IPV shortage, the program should ensure the availability of ID devices to facilitate administration of fractional-dose ID IPV for outbreak response.
- WG concluded that sufficient number of tOPV campaigns with high coverage is the key to reduce the risk of type 2 VDPV emergence. In this regard, WG expressed concern over the SIAs calendar of Pakistan as there is only one tOPV nationwide vaccination round (March 2016) within six months before the OPV2 withdrawal (with two sub-national tOPV SIAs in October 2015 and February 2016 targeting about 50% of the target population aged less than five years).
- The program should be prepared for outbreaks, so that an outbreak response can be launched within two weeks of confirmation of a case. This requires preparation for rapid field investigation, strengthening surveillance, accelerating laboratory processing, and communication with countries and the scientific and public health community ahead of time.

Preparation for OPV type 2 withdrawal

The WG reviewed the progress towards OPV type 2 withdrawal, scheduled in the second half of April 2016. IPV introduction is on track in the highest priority countries. So far 149 countries already use IPV and all remaining 45 countries are planning to introduce IPV in 2016. There are 20 tier 3 and 4 countries and two tier 2 countries (Equatorial Guinea and Indonesia) that will introduce IPV after April 2016. By the end of 2015, more than 80% of the global birth cohort was living in countries in which IPV has been introduced in the routine immunization schedule. The use of bOPV has been approved by 123 of 151 OPV-using countries due to carry out the tOPV-bOPV switch, with the remaining 28 countries expected to approve bOPV use by April 2016. Switch plans have been developed by all tier 1-3 countries, with financial support provided to selected countries to ensure on-time implementation.

WG decisions/recommendations

- The WG acknowledged the strong and sustained progress toward addressing the readiness criteria for the tOPV-bOPV switch.
- The WG expressed concern that the IPV supply shortage will likely persist into 2017, and encouraged the program to closely monitor the supply and demand to ensure IPV availability in countries, and minimize stock-outs.
- The WG emphasized the importance of ensuring that the scientific and medical communities are aware of the switch and its rationale

Containment

The WG reviewed the status of GAP III implementation. Since the last WG meeting in October 2015, there has been significant progress, particularly: 1) communication to the scientific community on regions, countries and facilities; 2) targeted engagement with countries at risk of lagging behind (especially 95 countries which have not completed reporting on WPV2/VDPV2); and 3) intensified efforts for GAP III implementation. WHO is establishing a Containment Advisory Group (CAG) to provide further guidance on the handling of potentially-infected specimens, essential research projects, and interim risk reduction measures. WHO is strengthening its headquarters containment team and has conducted regional GAPIII implementation and certification workshops in AFR, EUR, SEAR, EMR and WPR. (Additional AFR, AMR and EUR workshops are scheduled in May

2016). Phase I implementation continues to achieve destruction of WPV2 and cVDPV2 stocks in advance of the switch. , Member States are expected to report on disposition of OPV2/Sabin2 materials as of July 2016.

WG decisions/recommendations

- The WG emphasized the importance of polio facilities destroying WPV2 and cVDPV2 materials before the time of the tOPV-bOPV switch in April 2016, except those that plan to become poliovirus-essential facilities and expect to be officially designated as such by their respective national authority for containment.
- The program should urgently engage countries hosting non-poliovirus facilities that handle potentially infectious material, and support them in their efforts to complete the identification, destruction or containment of Sabin 2 materials

Topic 3: Future immunization policy

Global withdrawal of tOPV will take place in April 2016. With the planned interruption of WPV transmission during 2016, it is expected that the withdrawal of all OPV should take place around 2020. There are important questions to address about immunization policy beyond this time. National programs, manufacturers and donors need to start discussions and preparations. Remaining uncertainties that need to be addressed include: polio program timelines, the immunogenicity (humoral and mucosal) of one or two IPV doses under different schedules, projected vaccine supply, vaccine costs (and funding), and countries' willingness of countries to continue to pay for IPV and polio risk management measures.
The WG began discussion of this topic and identified topics for further discussions at future meetings. It is likely that vaccination against polio will need to continue into the 2020-2030 period. There will be a need for global level agreement on how long polio vaccination should continue, though countries may choose to diverge from this. Advice by SAGE will be needed on the criteria that countries should meet before stopping vaccination (e.g., meeting of surveillance performance standards, appropriate implementation of containment measures). More work is needed to define the number, schedule and formulation of IPV doses, and further analysis is needed of the vaccine supply situation and vaccine costs and affordability.
The WG reviewed the current IPV market dynamics. New suppliers are likely to enter the market around 2018-2020, likely alleviating the global demand shortages of IPV. Several suppliers are also working on hexavalent vaccine that includes IPV and whole-cell pertussis vaccine, but all manufacturers face significant challenges in terms of manufacturing logistics, capacity, and cost-of-goods.

WG decisions/recommendations

- To secure the long-term success of polio eradication, vaccination will likely need to continue after OPV withdrawal, possibly for at least 5-10 years, because of risks associated with iVDPVs, and containment facilities.
- The program should develop the criteria for countries and regions to stop poliovirus vaccination (e.g. surveillance capacity and sensitivity, , no evidence of iVDPVs).
- The program should continue to monitor the vaccine supply situation, including IPV availability and affordability.
- The WG proposes to develop a recommended high-level policy direction during 2016 and to finalize its recommendations for full SAGE consideration in 2017.

Topic 4: iVDPV epidemiology and management strategy

The WG reviewed an update on the current known epidemiology of iVDPV infections. Currently, there are 107 iVDPV patients in the WHO registry, who are or have excreted iVDPV. There has been a substantial increase in detected cases (with two divergent trends – an increase from middle-income countries and a decrease from high-income countries). In terms of geographical distribution, there is clustering in the Middle East – possibly due to co-sanguinity. There is substantial underreporting (particularly for iVDPV excretors without acute flaccid paralysis). Type 2 polioviruses are the predominant cause of iVDPV cases, causing >60%% of all cases. These iVDPVs might constitute a significant risk in triggering outbreaks among under-immunized populations post-OPV cessation. This risk appears to be concentrated in lower and upper middle-income countries (e.g. India, Nigeria, Indonesia, and Egypt).

The WG then reviewed the progress of the development of antivirals against poliovirus. Early clinical studies have found that Pocapavir (V-073) is safe and effective in clearing excretion, but the rate of emergence of resistance is considerable. Therefore, the Polio Antivirals Initiative (PAI) is now preparing to study the combination of Pocapavir and one more compound (V-7404).

WG decisions/recommendations

- The WG recognized that iVDPVs can pose a significant risk to maintaining global polio eradication. While iVDPV excretors are rare and the risk of transmission is low, any transmission could have significant consequences, especially after OPV withdrawal.
- The WG requested the WHO secretariat to develop options for enhancing surveillance sensitivity for detecting iVDPVs and discuss modelling of risk estimates during the next face-to-face meeting of the SAGE WG.

Summary and next steps for the SAGE Working Group

The 11th meeting of the SAGE WG reviewed the final stage of preparation for OPV type 2 withdrawal and started its discussions on future immunization policy. The WG also reviewed the epidemiology of iVDPV and the development of antiviral drugs and learned about published modelling results that explored iVDPV risks and the potential benefits of antiviral drugs.

The WG requested a follow-up conference call in February or March 2016, particularly to receive a further update on: i) the progress on interrupting the cVDPV2 outbreak in Guinea and Myanmar; and ii) IPV supply situations.

(Appendix-1: Summary of discussions with modelling groups)

Conclusion: Risk of VDPV Emergence

- **Risk of emergence:** There is high probability that at least 1 cVDPV will emerge within 12 months of the switch. High quality tOPV SIAs before the switch (i.e. at least three times with at least 80% coverage) will reduce the risk of emergence significantly.
- **Timing of emergence:** The risk is greatest in the first year and declines thereafter. However, the consequences are greater, the longer the time between the switch and emergence. This presentation only focuses on the risks within 12 months of the switch.
- **Risk factors**: Low type 2 immunity is greatest risk factor. (Other risk factors include birth rate, population size and density, low RI coverage, failure to reach unvaccinated children in pre-switch SIAs, and other conditions associated with high levels of transmission, particularly fecal-oral route).
- **Geography**: The biggest risk exists in AFRO and some parts of EMRO, SEARO and WPRO. Pakistan remains a concern because Pakistan plans only one national tOPV campaign in 2016, prior to the switch in April.
- **Risk of aVDPV evolving to cVDPV:** Historically, most aVDPVs died out without program intervention in the context of relatively high vaccination rates during polio eradication. More aggressive response to aVDPV is needed, the longer the interval from the switch, occurrence in an area with prior cVDPV emergence, substantial genetic deviation from parent Sabin virus (nt deviations, recombination with class C enterovirus).

Conclusion: cVDPV2/WPV2 Response Strategy

- **Optimal number of SIA rounds**: 4 minimum, more may be needed in high R0 settings.
- **Speed of SIAs**: First SIA within 2 weeks of detection is beneficial even with suboptimal coverage. Reaching high coverage is critical in subsequent rounds (esp. populations in low RI coverage).
- **Interval of SIAs**: Short (2 weeks) interval is better if not compromising the coverage (program feasibility must be considered).
- **Target age group**: 0-5 years old. Unless there is evidence of circulation among older persons
- **Target population**: A minimum of 2 million children is adequate in most places if the program can achieve high coverage. Consider expanding the scope further if there is evidence of extensive circulation (higher nt changes) and the program can attain high coverage.
- **Use of tOPV**: Although the tOPV and mOPV2 have similar immunogenicity against type 2, use of tOPV in post-switch is not possible because all tOPV is removed from the field and destroyed. Simultaneous bOPV and mOPV2 might be considered in areas at risk for WPV1/3.

Conclusion: Role of IPV

- **Benefit of IPV**: IPV is useful in boosting intestinal immunity among OPV-primed children. Therefore, within first 12 months after the switch, the program should include IPV in the second SIA. Special attention should be paid to achieving high coverage. With time, IPV alone is less useful to prevent transmission, but will reduce paralytic disease.
- **Timing of IPV**: IPV should be used in the second SIA to assure adequate time for planning and high coverage without compromising the coverage and timing of OPV rounds. High OPV and IPV coverage are essential.
- **Target of population**: same as mOPV2 (2 million in core areas). If IPV supply is adequate, consider additional 2 million in the surrounding areas. Fractional doses of IPV can be used if ID devices are available.
- **Effectiveness of ring vs. transit strategy**: unable to fully assess at this time. A country should select the strategy based on in-depth investigation of epidemiology and expected coverage. International Health Regulations may require vaccination of travelers from/to infected areas.

SAGE Polio Working Group

3 March 2016

Conference Call Notes

INTRODUCTION

A SAGE Polio Working Group (WG) teleconference was held on 3 March 2016 to discuss follow-up items from its January 2016 meeting. The call was attended by the following WG members: Yagob Al-Mazrou (Chair), Peter Figueroa , Walter Orenstein, Walter Dowdle, T Jacob John, Elizabeth Miller, Kimberly Thompson, Hyam Bashour and Antoine Kabore. Francis Nkrumah, Zulfiqar Bhutta and Nick Grassly 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 epidemiology of circulating vaccine derived poliovirus (VDPV) type 2 (**Information**)
2. Review the preparations for OPV2 withdrawal (**Information**)
3. Discussion on reporting type 2 case detection under IHR (**Endorsement**)
4. Use of fractional ID IPV for campaign and routine immunization (**Endorsement**)

PRESENTATIONS, DISCUSSIONS AND CONCLUSIONS

TOPIC 1
Review the current epidemiology of cVDPV type 2

The WG reviewed the current status of cVDPV type 2. In 2015, cVDPV type 2 cases were reported in Nigeria, Guinea, and Myanmar. Nigeria conducted multiple tOPV SIAs in 2015, which appear to have stopped the transmission of cVDPV2s there. The outbreak response in Myanmar is on track; with no cVDPV type 2 cases after 5 October 2015, four tOPV SIAs completed as of March 2016, and a fifth SNID currently under consideration. With high quality tOPV SIAs and high routine immunization coverage, the probability of outbreak continuation in Myanmar beyond switch or geographic expansion seems low. Guinea experienced several challenges in responding to the cVDPV2 outbreak, including competing national priorities due to Ebola that led to decreased quality of polio SIAs and surveillance. To date Guinea has reported 8 confirmed cases of a newly emerged cVDPV2 with onset between 30 August 2014 and 14 December 2015, in Kankan Region, in eastern Guinea. In response, an emergency outbreak plan has been implemented with support from GPEI, including: Outbreak Assessment with focus on surveillance with active case searching in Guinea and neighbouring Ebola-affected countries. Guinea has conducted and is planning tOPV NIDs to stop transmission, but some risk of continuation of circulation of cVDPV2 beyond the switch exists for Guinea, with possibility of spread to neighbouring areas.

In addition, a VDPV2 case was recently reported from Democratic Republic Congo with 16 nt changes with onset on 13 January 2016. The investigation is ongoing. Urgent measures are underway to ensure three SIAs are implemented prior to switch. If this outbreak continues beyond the switch, the program will use mOPV2 for the outbreak response rounds after the switch. The DRC may move its national switch date to the end of the switch window, but this outbreak will not delay the global switch from tOPV-bOPV that will occur during April 15-30.

WG comments

- Agreed that outbreak in Myanmar is unlikely to pose any threat to the global switch.
- Expressed concern about the situations in Guinea and DRC, and encouraged the WHO to accelerate the implementation of response in these countries, including delaying the switch towards the end of two weeks switch period.

- Expressed concern that Pakistan still appears to present a risk for cVPDV type 2 cases after the switch due to the relatively low number of tOPV SIAs conducted there in the run up to the switch.

TOPIC 2
Global preparations for OPV2 withdrawal

The WG reviewed the different aspects of preparations for the OPV2 withdrawal.

IPV introduction and supply

To date, 92 countries introduced IPV since January 2013, including all 17 tier 1 countries and 14/19 tier 2 countries. Due to the IPV supply shortage, 20 low-risk countries and one self-procuring country (Indonesia) will introduce IPV after the switch.

As of early February 2016, Bilthoven Biologicals, one of the two IPV suppliers to the GPEI, informed UNICEF SD and PAHO RF that they are facing production problems and will need to reduce again the amount of IPV they are able to provide.

- For UNICEF SD: Overall reduction of 1m doses in 2016, and a delay in provision of 6m doses (Only 4.6m out of the planned 10.6m will be delivered before the switch).
- For PAHO RF: Overall reduction of 2.8m doses in 2016, with most being provided only as of Q3 (post switch). In addition, PAHO still has pending orders from 2015 totalling 1.4 million doses which will hopefully be delivered by May 2016.

As a result, seven low risk countries (tier 3 and 4) will not be able to introduce IPV before the first quarter of 2017. In addition, some shipments of IPV to countries that have already introduced in their programme will need to be delayed:

- by 1-3 months for 10 Tier 2 (higher risk) countries, with limited risk of disruption of their programme
- by 2-6 months for 12 low risk countries (tier 3 and 4), with a high risk that these countries will face stock outs

IPV supply shortage is likely to continue over 2016-18; it may be limited further for the 5-dose and 1-dose presentation from Bilthoven Biologicals.

Given the unreliability of the IPV manufacturers to meet supply projections to date, the GPEI has already started working on further contingency plans.

Regulatory approval of bOPV for routine use
To date, 134/144 countries approved the use of bOPV for routine (including all countries SEARO and AFRO). The program is closely following up with the remaining 10 countries, and no issues are expected.

Environmental surveillance
The global plan to expand environmental surveillance is on track in the majority of countries, with the expansion in DRC being implemented by April 2016, and Mali by July 2016. Unfortunately, Yemen and Somalia will not be able to implement the plan due to unstable security conditions in country.

Containment
The implementation of GAP III phase I shows substantial progress for most regions, with recent completion of phase I in WPRO with all reports received. Unfortunately, no reports have been received yet from PAHO.

Country preparation
All tier 1, 2, and 3 countries have developed their switch plans. Distribution of financial support to selected (67) countries is on track; 16/17 Tier 1, 17/19 Tier 2 countries have received financial support. 24 countries were identified for technical assistance to support monitoring activities during the validation of the switch.

WG comments

- WG noted the update and encouraged WHO to continue to monitor the IPV supply situation and

explore different options to mitigate the IPV supply shortage

TOPIC 3
Discussion on reporting type 2 case detection under IHR

Under the International Health Regulations (IHR) (2005), a notifiable case of poliomyelitis due to wild-type poliovirus is defined as "a suspected case with isolation of wild poliovirus in stool specimens collected from the suspected case or from a close contact of the suspected case." This definition does not include VDPV nor virus isolation from the environmental samples, so WHO added the VDPV and Virus detected from non-human sources (e.g. environmental samples) to the WHO surveillance case definition for notification under the IHR on the grounds that such events are "unusual or unexpected and may have serious public health impact."

After OPV2 withdrawal, it is critical to ensure post-switch that all type 2 polioviruses are notified, including Sabin 2, in addition to VDPV and WPV. WHO proposed that type 2 Sabin virus be added to the WHO surveillance case definition as a notifiable event in addition to WPV and VDPV after 1 August 2016.

WG comments

- WG endorsed the proposal to amend and broaden the WHO surveillance case definition to include type 2 Sabin in addition to wild and vaccine-derived PV
- WG recommended that WHO communicate (after the switch and prior to 1 August) the need for Member States to report Sabin type 2

TOPIC 4
Use of fractional ID IPV

Due to the IPV supply shortage, the WG considered an option of use of fractional intradermal (ID) IPV for both outbreak and routine immunization use.

SAGE previously reviewed the evidence regarding the use of ID and recommended to accelerate the development of an ID IPV option (April 2012). SAGE WG revisited it again in September 2015, welcoming the progress of the development of ID IPV and encouraged the GPEI to accelerate the development and introduction of ID IPV devices.

Recent studies from Bangladesh[1] and Cuba[2] demonstrated that the immunogenicity of two fractional doses of IPV is superior to one full dose at the ages given in the studies. In Cuba, two fractional (1/5) doses of ID IPV given at 4 and 8 month induced 98% seroconversion rate against type 2, which is much higher than one full dose IM IPV given at 4 month (63%). Likewise, in Bangladesh, two fractional doses of ID IPV given at 6 and 14 weeks in Bangladesh induced 81% seroconversion against type 2 vs. 39% among those with one full dose IM IPV at 6 weeks. In both studies, two fractional doses induced substantially higher antibody titers against type 2 than one full dose. The use of fractional ID IPV is dose-sparing, with the 2 fractional doses using 2/5 of the full dose (i.e., 60% dose-sparing), although it requires an additional injection and the associated injection supplies and trained personnel.

Also, a recent Cuba study indicated that one ID IPV dose was as effective as an intramuscular (IM) IPV to boost the immunity among OPV-immunized adults (with the non-inferiority criteria of <10% at days 7, 28, and 56)[3].

Based on these data and the ongoing IPV shortage, the recent WHO position paper on polio vaccine (to be published in March 2016) states:

[1] Anand A et al. Early priming with inactivated poliovirus vaccine (IPV) and intradermal fractional dose IPV administered by a microneedle device: A randomized controlled trial. Vaccine. 2015 Nov 27;33(48):6816-22

[2] Resik S et al. Priming after a Fractional Dose of Inactivated Poliovirus Vaccine. N Engl J Med 2013;368:416-24.

[3] Resik S et al. (unpublished data)

In the context of an IPV shortage, countries could consider instituting a 2-dose fractional dose schedule which could ensure that all eligible infants receive IPV, is dose-sparing and results in better immunogenicity than a single full dose of IPV. To ensure early protection a schedule of fractional doses administered at 6 and 14 weeks may be considered. The two fractional doses should be separated by a minimum interval of 4 weeks. Fractional-dose IPV may be particularly appropriate for outbreak response if supplies are limited.

Recently, the India Expert Advisory Group (IEAG) recommended that 7 states in India will introduce a schedule of two fractional doses of IPV (before or shortly after the switch) at 6 and 14 weeks.

There are a few other studies available/ongoing/planned in Pakistan, Sri Lanka and Cuba

- ***Cuba:*** Use of different ID IPV devices indicated Pharmajet needle-free jet injector can similar immunity to BCG needle[4] (study completed)
- **Pakistan**: Use of needle adapters for facilitating intradermal administration (with Star syringe, West needle adapters vs. BCG needle) (study ongoing)
- **Sri Lanka**: Boosting of mucosal immunity 10-12 year olds with fractional-dose IPV (in ethical review)

WG comments

- Confirmed that the proposed schedule of two fractional IPV doses can induce equal or better immunity than current one full-dose schedule
- Endorse the proposed strategy to use fractional ID IPV in campaigns and routine schedule to pro-actively address IPV supply shortage:
    - The program should use one fractional dose in outbreak response; it provides good seroconversion in naïve infants and protects them from paralysis, and it boosts humoral (and likely boosts mucosal) immunity in older previously OPV-vaccinated children
    - Selected countries or states within a large country (e.g. those with strong routine immunization system) may also consider two fractional doses in the routine schedule (e.g. at 6 and 14 weeks for early protection)
- Encourage that countries introducing two fractional ID IPV into their routine schedule assess the operational feasibility and challenges

[4] S. Resik et al. Immune responses after fractional doses of inactivated poliovirus vaccine using newly developed intradermal jet injectors: a randomized controlled trial in Cuba. Vaccine. 2015 Jan 3;33(2):307-13

An interim meeting of the mini India Expert Advisory Group (IEAG) for Polio Eradication
Delhi, India, 26 February 2016

Conclusions and Recommendations

An interim meeting of the mini India Expert Advisory Group (IEAG) for polio eradication was convened on 26 February 2016 in Delhi, with the following objectives:

1. To review the IPV supply constraints in India and associated risks;
2. To assess the need for any adjustments in India to the implementation of the globally coordinated switch from trivalent oral poliovirus vaccine (tOPV) to bivalent oral poliovirus vaccine (bOPV) in April 2016
3. To make recommendations on strategies to mitigate the risks related to the withdrawal of the type 2 component of tOPV

The meeting was chaired by Mr B P Sharma, Secretary (Health and Family Welfare), Ministry of Health and Family Welfare (MoHFW), Government of India, and co-chaired by Dr Jagadish Deshpande, Former Director, Enterovirus Research Centre (ICMR), Mumbai. A list of IEAG members and the special invitees that attended the meeting is annexed. The special invitees included Mr Michel Zaffran, Director, Polio Eradication Department, World Health Organization, Geneva; Dr Roland Sutter, Coordinator, Research, Policy and Product Development, Polio Eradication Department, World Health Organization, Geneva, and; Mr Ian Lewis, Contract Specialist, UNICEF Supply Division, Copenhagen.

The IEAG met in the context of two urgent developments for India and the world:

- A further reduction in the quantities of IPV available to India in 2016 and 2017;
- The global switch from trivalent oral poliovirus vaccine (tOPV) to bivalent oral poliovirus vaccine (bOPV) in April 2016

The IEAG was posed the following questions by the Government of India:

1. Can additional IPV supplies be mobilized from global resources to meet India shortfalls so that IPV can be introduced in all 36 states/UTs before the switch?
2. Should India defer the switch until IPV is introduced in all states/UTs?
3. Should India implement the switch in April 2016 without introducing IPV in six low risk states? If so, what are the possible risks and mitigation strategies?

Background

In October 2015, the Strategic Advisory Group of Experts on immunization (SAGE) to WHO met and reviewed type 2 vaccine-derived poliovirus (VDPV2) epidemiology and all readiness criteria for the switch. SAGE reaffirmed April 2016 for the globally coordinated withdrawal of the type 2 component of OPV, by switching from use of tOPV to bOPV.

Initially a pre-requisite for the switch was for all OPV-only using countries to introduce at least one dose of IPV before the end of 2015. Due to technical challenges encountered in

the rapid scale-up of IPV production required to meet this timeline, there is reduced availability from manufacturers on all presentations.

In assessing all criteria for the switch and confirming the switch in April 2016, SAGE emphasized that in the event of further reductions in IPV supply, the switch date will not be changed. Accordingly, SAGE endorsed a risk-based approach to prioritizing the allocation of available supply, and outlined its rationale to risk management.

India has also experienced changes to timelines and reduced volumes of IPV. As of February 2016, 28.14 million doses have been assured through Gavi, and repeat tenders for domestic procurement for the period from October 2016 to March 2018 have resulted in an offer of 24 million doses (51% of the total requirement of 47.42 million doses) leaving a shortfall of 23.42 million doses. India has already introduced IPV in six large, high-risk states since 30 November, 2015.

Preparations to implement the switch are well on track in India – commitment to this was confirmed – with the National Switch Date set to 25 April 2016. However, with the latest setbacks to IPV supply, India expects to be able to sustain IPV in only 30 states/UTs until March 2018, or in 36 states/UTs until May 2017.

Guidance was sought on the possibility of mobilizing additional IPV supplies, deferring or adapting the implementation of the OPV switch, and risk mitigation strategies related to implementing the switch without having IPV introduced in 6 states/UTs.

IEAG Conclusions and Recommendations

The questions posed to the IEAG were discussed at length, with a focus on risk mitigation strategies related to the withdrawal of the type 2 component from tOPV.

The recommendations below aim to answer the questions posed to the IEAG by the Government of India and to outline the strategies and activities needed to mitigate the risks associated with the OPV switch, in the absence of IPV in routine immunization in 6 states/UTs.

1. *Can additional IPV supplies be mobilized from global resources to meet India shortfalls so that IPV can be introduced in all 36 states/UTs before the switch?*

It was confirmed by UNICEF Supply Division and WHO that there is no additional IPV available from any of the IPV manufacturers, despite extensive efforts. Both UNICEF Supply Division and WHO have been engaged in frequent high level discussions with manufacturers since mid-2015, when there were early indications of challenges in scaling up production. .

The IPV supply constraints are now global, affecting all countries no matter their procurement mechanism (UNICEF, PAHO Revolving Fund, or self-procuring). Specifically, 28 low risk countries will see delayed IPV deliveries in 2016, with seven of them being delayed until the first quarter of 2017.

Additional supply for India is unlikely to materialise before 2018-2019, however the situation is being closely monitored on an ongoing basis and should additional doses become available, priority will be given to India.

2. *Should India defer the switch until IPV is introduced in all states/UTs?*

In October 2015, SAGE reaffirmed that the switch should proceed in April 2016, inspite of the supply constraints and even if further IPV supply constraints were to materialise. SAGE also emphasized that the risk of continued tOPV use outweigh risks of withdrawing the type 2 component.

The IEAG revisited the rationale for IPV introduction as a risk mitigation tool, noting:

- One dose of IPV will induce an immunity base to poliovirus type 2 and strengthen immunity against types 1 and 3
- The immunity base offered by IPV would be expected to greatly reduce the consequences of poliovirus type 2 exposure (in terms of paralytic disease), post-switch
- In the case of an outbreak due to type 2 poliovirus, post-switch, a second dose of polio vaccine (monovalent type 2 OPV or IPV) should rapidly close any remaining immunity gaps.

The IEAG agreed that the risk of continuing with the use of type 2 OPV high given the fact that India has been polio free for almost 5 years and the risk of cVDPV caused by the type 2 vaccine virus is substantial. The IEAG, therefore, recommended that **India should proceed with the switch in April 2016 in the entire country**, which in the current context, presents a much lower risk than the pending introduction of IPV in 6 states/UTs.

3. *Should India implement the switch in April 2016 without introducing IPV in 6 low risk states? If so, what are the possible risks and mitigation strategies?*

The IEAG noted that India has already conducted two NIDs with tOPV in January and February 2016 and discussed at length the various complementary approaches to risk mitigation, which are summarized as follows:

- Maintain high type 2 immunity before the switch, through the use of tOPV SIAs, in areas with sub-optimal routine coverage.
- Maintain surveillance systems through AFP surveillance and environmental sampling, to help ensure detection of any type 2 events after the switch.
- Use of IPV as a fractional dose, through administration of two intradermal (ID) fractional doses, representing one-fifth of the full dose, therefore enabling optimum use of the available supply to cover all 36 states/UTs in India with IPV.
- Update outbreak preparedness and response plans in all states/UTs to manage any outbreaks in the post-switch period

Specifically in relation to the fractional dose, data from studies to date in Cuba and Bangladesh were presented, demonstrating the “prime-boost” model of doses at 6 weeks and 14 weeks, and offering better protection than a single full dose. The IEAG was also presented with a preview of the text of the revised WHO Position Paper on polio (in press; publication date 25 March) relating to the use of fractional dose IPV.

The text reads "*…As an alternative to the intramuscular injection of a full dose of IPV, countries may consider using fractional doses (1/5 of the full IPV dose) via the intradermal route, but the programmatic cost and logistic implications of this option should be considered. In the context of an IPV shortage, countries could consider instituting a 2-dose fractional dose option which could ensure that all eligible infants receive IPV, is dose-sparing, and results in better immunogenicity than a single full dose of IPV…."*

As a risk mitigation strategy, in the absence of sufficient IPV supply, the IEAG recommended that the **Government of India should consider implementing a routine immunization schedule of 2 fractional doses of IPV, administered at 6 weeks and 14 weeks, in 6 or 7 of the high performing states/UTs.** The over-riding objective is to ensure administration of IPV to all infants (before or as early as feasible after the switch). While potentially more programmatically demanding and requiring an off-label use, the fractional dose has many advantages, as it will reduce costs, offer better immunogenicity than a single full dose of IPV, and help to ensure that all eligible infants in India receive IPV.

The IEAG further recommended that the use of fractional dose of IPV in selected states of India should be re-assessed in 12 months and a decision to continue in the six states or expand to additional states should be taken based on the lessons learnt from this experience and the supply position at that point in time. The IEAG also recommended that cross sectional sero-surveys and prospective cohort studies should be conducted to better understand the immunogenicity and protection provided by the two fractional doses in the Indian setting, and to guide further decision making on the continuation and/or expansion of the use of fractional dose of IPV in the country. Operational studies to assess the challenges associated with the administration of fractional dose as well as wastage studies were also recommended by the IEAG.

List of Participants

1	Shri B.P. Sharma, Secretary (Health & Family Welfare), MoHFW
2	Shri C.K. Mishra, Additional Secretary & Mission Director, MoHFW
3	Dr. Rakesh Kumar, Joint Secretary, RCH programme, MoHFW
4	Dr. Pradeep Haldar, Deputy Commissioner, MoHFW
5	Ms. Bindu Sharma, Director (RCH), MoHFW
6	Dr. Jagadish Deshpande, Director, ERC, Mumbai
7	Dr. Devender Taneja, Prof. of PSM, MAMC, Delhi
8	Dr. N.K. Arora, Coordinator- Polio Eradication Certification Committee
9	Mr. Deepak Kapur, Chairman, Rotary International- India
10	Dr. Henk Bekedam, WCO-India
11	Mr. Michel Zaffran- WHO, HQ
12	Dr. Roland Sutter- WHO, HQ
13	Ms. Lisa Menning, WHO, HQ
14	Dr. Sunil Bahl, WHO, SEARO
15	Dr. Pankaj Bhatnagar, WHO-NPSP
16	Mr. Ian Lewis, UNICEF
17	Mr. Suvi Rautio, UNICEF-India
18	Dr. Pramod Jog, IAP
19	Dr. Sunil Gupta, NCDC, Delhi
20	Dr. Arindam Ray, BMGF
21	Dr. Nivedita Gupta- ICMR
22	Dr. Rashmi Arora, ICMR
23	Dr. Priti Chaudhary, WHO-NPSP

IPV and the OPV switch: risk mitigation

18 March 2016

Background

- In March 2014, UNICEF issued awards to two manufacturers for the supply of IPV in 1, 5 and 10 dose vials and long term supply agreements were established through to 2018
- Due to technical challenges in scaling up IPV bulk production and the associated quality control testing and releases, there is now reduced availability from both manufacturers for all presentations
- The IPV supply constraints are expected to remain dynamic until 2018 and will continue to be closely monitored
- All possible steps are being taken in order to limit the number of countries impacted by the delays and minimise the consequences of this unforeseen situation

Recap on the role of IPV

- One dose of IPV will induce an immunity base (sero-conversion and/or priming) to poliovirus type 2, and boost immunity against types 1 and 3
- This immunity base is expected to reduce the risk of paralytic disease following poliovirus type 2 exposure
- In case of epidemic transmission of poliovirus type 2, a second dose of polio vaccine (mOPV2 or IPV) should rapidly close any remaining immunity gaps and induce mucosal immunity (reducing the risk of community transmission)
- Therefore IPV primarily serves as a risk mitigation tool

3

Review by SAGE in October 2015

- SAGE reaffirmed its recommendation that the globally synchronized switch should take place in April 2016, and confirmed the switch window **from 17 April to 1 May 2016**
- **SAGE concluded that the risks of continued use of tOPV is greater than the risks of switching to bOPV** in multiple respects: epidemiological, programmatic, political, and financial
- SAGE emphasized that even in the event of further changes in IPV supply, the switch date will not be changed
- **SAGE also confirmed that all countries must implement the OPV switch in April 2016, even in instances where IPV introduction had not occurred prior to the switch**

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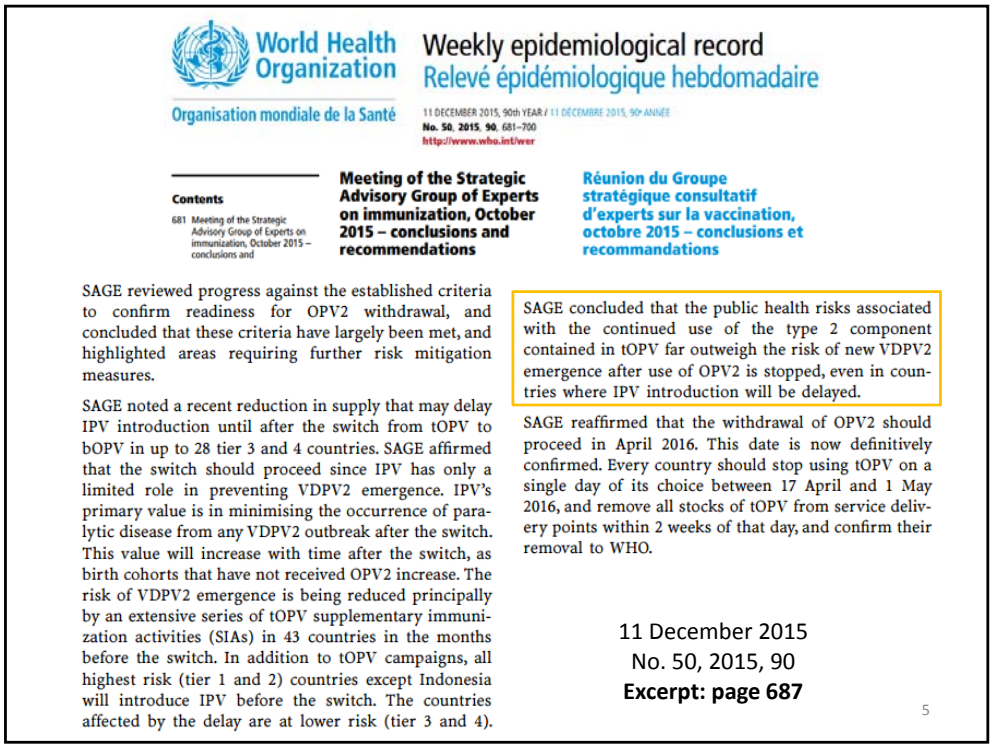

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

11 DECEMBER 2015, 90th YEAR / 11 DÉCEMBRE 2015, 90e ANNÉE
No. 50, 2015, 90, 681–700
http://www.who.int/wer

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Meeting of the Strategic Advisory Group of Experts on immunization, October 2015 – conclusions and recommendations

Réunion du Groupe stratégique consultatif d'experts sur la vaccination, octobre 2015 – conclusions et recommandations

SAGE reviewed progress against the established criteria to confirm readiness for OPV2 withdrawal, and concluded that these criteria have largely been met, and highlighted areas requiring further risk mitigation measures.

SAGE noted a recent reduction in supply that may delay IPV introduction until after the switch from tOPV to bOPV in up to 28 tier 3 and 4 countries. SAGE affirmed that the switch should proceed since IPV has only a limited role in preventing VDPV2 emergence. IPV's primary value is in minimising the occurrence of paralytic disease from any VDPV2 outbreak after the switch. This value will increase with time after the switch, as birth cohorts that have not received OPV2 increase. The risk of VDPV2 emergence is being reduced principally by an extensive series of tOPV supplementary immunization activities (SIAs) in 43 countries in the months before the switch. In addition to tOPV campaigns, all highest risk (tier 1 and 2) countries except Indonesia will introduce IPV before the switch. The countries affected by the delay are at lower risk (tier 3 and 4).

SAGE concluded that the public health risks associated with the continued use of the type 2 component contained in tOPV far outweigh the risk of new VDPV2 emergence after use of OPV2 is stopped, even in countries where IPV introduction will be delayed.

SAGE reaffirmed that the withdrawal of OPV2 should proceed in April 2016. This date is now definitively confirmed. Every country should stop using tOPV on a single day of its choice between 17 April and 1 May 2016, and remove all stocks of tOPV from service delivery points within 2 weeks of that day, and confirm their removal to WHO.

11 December 2015
No. 50, 2015, 90
Excerpt: page 687

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Risk management rationale

(endorsed by SAGE in October 2015)

- **IPV has only a limited role in preventing the emergence of type 2 vaccine-derived polioviruses** (VDPV2). IPV's primary value is in minimizing the occurrence of paralytic disease from any VDPV 2 after the switch
- The majority of countries affected by the delay are in low risk tiers 3 and 4. **Population immunity against type 2 is high in these countries** (due to consistently high routine immunisation coverage) so the risk of VDPV2 emergence and spread is minimal
- The risk of VDPV2 emergence is **principally reduced by ensuring high coverage, and may include high quality tOPV SIAs** before the switch in countries or communities with immunity gaps
- In addition to tOPV SIAs, almost all **highest risk (tier 1 and tier 2) countries will have introduced IPV** in routine immunization before the switch
- **A global stockpile of mOPV2 (which is WHO prequalified) and IPV** is available for outbreak response in the event of VDPV2 detection in any country after the switch. Countries should have a mechanism in place for emergency authorization of mOPV use in an outbreak

EPI POLIO GLOBAL ERADICATION INITIATIVE

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Allocation of available supply

(endorsed by SAGE in October 2015)

There are four criteria used to determine the classification of each country, and therefore its prioritization for the allocation of IPV.

Countries are considered to be in a higher risk tier if:

- The transmission of wild poliovirus has not yet been interrupted
- The country has a history of cVDPV outbreaks
- There are consistently low levels of routine immunization coverage (and therefore population immunity to type 2)
- The country shares borders with higher risk countries

→ Based on these criteria, countries considered as low risk may see delays in **IPV introductions** or **resupply shipments** for routine programmes.

EPI POLIO GLOBAL ERADICATION INITIATIVE

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If IPV introduction is delayed

- **Optimize type 2 immunity through tOPV SIAs** in locations with sub-optimum routine coverage, in the lead-up to the switch (advisable to all countries)
- **Coordinate switch implementation in a highly effective and timely manner,** to ensure no tOPV is used after the switch window
- **Enhance** AFP surveillance and environmental sampling
- **Ensure that preparations for IPV introduction are completed in advance**, so that IPV roll out can start as soon as the vaccine becomes available
- **Plan for the vaccination of any eligible infants who missed a scheduled dose of IPV after the OPV switch in April 2016**, e.g. came for DTP3 after switch, but IPV was not available
- **Prepare a response plan** so that in the unlikely situation that a type 2 cVDPV outbreak occurs, it can be addressed and ended as soon as possible

EPI POLIO GLOBAL ERADICATION INITIATIVE

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If IPV stock-outs may be expected

- **Closely monitor IPV stocks at all levels**, to balance stocks effectively to help prevent stock-outs, e.g. smaller and more frequent deliveries to lower levels to help with effective distribution of available supply
- **Ensure strict adherence to vaccinating children only in the target group**, e.g. one full dose of IPV at 14 weeks of age or the nearest following visit
- **Prioritize available supply to at-risk populations**, in the case of a potential IPV stock out
- **Apply the multi-dose vial policy**, to enable use of IPV with the vaccine vial monitor on the label up to 28 days after opening, to minimize wastage
- **Use vaccination cards and registers effectively** to record a missed dose of IPV, to facilitate later tracking and follow up

The option of a fractional dose of IPV

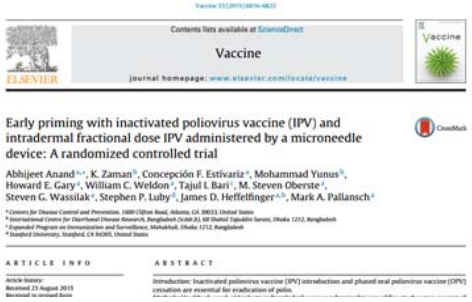
As an alternative to the intramuscular injection of a full IPV dose, **countries may choose the implementation of a two-dose fractional dose schedule** (using 1/5 of a full dose), via the intradermal route.

This may require:

- A review of clinical data at national level, by the NITAG or equivalent
- An assessment of the implications of the introduction of a fractional dose schedule from a programmatic perspective (e.g. supply of syringes, added training, time to roll-out, changes to the schedule, etc.)
- A decision by the NITAG and NRA to move to an off label use of IPV

For outbreak response, a fractional dose of IPV has been endorsed for use in conjunction with mOPV.

Two fractional doses versus one full dose


Vaccine

Early priming with inactivated poliovirus vaccine (IPV) and intradermal fractional dose IPV administered by a microneedle device: A randomized controlled trial


ORIGINAL ARTICLE

Priming after a Fractional Dose of Inactivated Poliovirus Vaccine

Author	Year published	Country	Schedule	One full-dose IPV	*Two fractional doses given intradermally*
Resik S	2013 Shown above	Cuba	IPV	63% (4 mos)	**98%** (4+8 mos)
Anand A	2015 Shown above	Bangladesh	IPV	39% (6 wks)	**81%** (6+14 wks)
Anand A	2016 In publication	Bangladesh	IPV	73% (14 wks)	

→ ***Two fractional doses are more immunogenic***

WHO Position Paper on Polio Vaccines

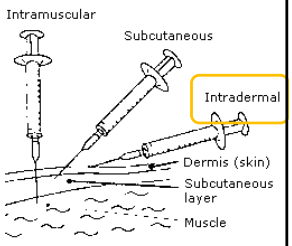
25 March 2016 (in press)

… *"As an alternative to the intramuscular injection of a full dose of IPV, countries may consider using fractional doses (1/5 of the full IPV dose) via the intradermal route, but the programmatic cost and logistic implications of this option should be considered.* ***In the context of an IPV shortage, countries could consider instituting a 2-dose fractional dose option which could ensure that all eligible infants receive IPV, is dose-sparing, and results in better immunogenicity than a single full dose of IPV.*** *This option may be particularly appropriate for outbreak response if supplies are limited."* …

EPI POLIO GLOBAL ERADICATION INITIATIVE

Fractional dose of IPV
Programmatic considerations

- Syringes and devices:
  - 0.1ml syringe is recommended (0.05ml for BCG)
- Timing in the schedule:
  - Starting at or after 6 weeks, with a minimum interval of 4 weeks, e.g. at 6 and 14 weeks
- Administration:
  - Added health worker training may be required
- Data recording:
  - Will involve adjustments to registers and records
- Communications:
  - Advance planning and careful messaging needed



Operational guidance to come!

EPI POLIO GLOBAL ERADICATION INITIATIVE

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For materials to support the implementation of IPV and the OPV switch:

http://www.who.int/immunization/diseases/poliomyelitis/endgame_objective2/en/

EPI POLIO GLOBAL ERADICATION INITIATIVE

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World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
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25 MARCH 2016, 91th YEAR / 25 MARS 2016, 91e ANNÉE
No 12, **2016**, **91**, 145–168
http://www.who.int/wer

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WORLD HEALTH ORGANIZATION
Geneva

ORGANISATION MONDIALE DE LA SANTÉ
Genève

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

03.2016
ISSN 0049-8114
Printed in Switzerland

Polio vaccines: WHO position paper – March, 2016

Introduction

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes. They summarize essential background information on diseases and vaccines and conclude with the current WHO position on the use of vaccines worldwide.

The position papers are designed to be used mainly by national public health officials and managers of immunization programmes. They may also be of interest to international funding agencies, vaccine advisory groups, vaccine manufacturers, the medical community, the scientific media, and the public. The papers have been reviewed by external experts and WHO staff, and are reviewed and endorsed by the WHO Strategic Advisory Group of Experts on Immunization (SAGE) (http://www.who.int/immunization/sage/en). The GRADE methodology is used to systematically assess the quality of available evidence. A description of the processes followed for the development of vaccine position papers is available at: http://www.who.int/immunization/position_papers/position_paper_process.pdf

In response to the World Health Assembly (WHA) declaration in 2012 that polio eradication constitutes a global public health emergency, the Polio Eradication and Endgame Strategic Plan 2013–2018 was developed. This plan includes the introduction of at least one dose of inactivated polio vaccine (IPV) into routine

Note de synthèse de l'OMS sur les vaccins antipoliomyélitiques – mars 2016

Introduction

Conformément à son mandat qui est de donner aux États Membres des conseils sur les questions de politique de santé, l'OMS publie une série de notes de synthèse régulièrement actualisées sur les vaccins et les associations vaccinales contre les maladies ayant un impact sur la santé publique au niveau international. Ces notes portent essentiellement sur l'utilisation des vaccins dans le cadre des programmes de vaccination à grande échelle. Elles résument les informations essentielles sur les maladies et les vaccins et présentent en conclusion la position actuelle de l'OMS concernant l'utilisation des vaccins dans le contexte mondial.

Ces notes de synthèse s'adressent avant tout aux fonctionnaires de la santé publique au niveau national et aux administrateurs des programmes de vaccination, mais elles peuvent également présenter un intérêt pour les organismes internationaux de financement, les groupes consultatifs sur les vaccins, les fabricants de vaccins, le corps médical, les milieux scientifiques et le grand public. Elles ont été examinées par des experts externes et des membres du personnel de l'Organisation, et sont analysées et approuvées par le Groupe stratégique consultatif d'experts (SAGE) sur la vaccination de l'OMS (http://www.who.int/immunization/sage/fr). La méthodologie GRADE est utilisée pour évaluer de manière systématique la qualité des éléments disponibles. Une description du processus suivi pour l'élaboration de ces notes est disponible à l'adresse: http://www.who.int/immunization/position_papers/position_paper_process.pdf.

En réponse à la déclaration de l'Assemblée mondiale de la Santé (WHA) de 2012 faisant de l'éradication de la poliomyélite une urgence de santé publique mondiale, le Plan stratégique pour l'éradication de la poliomyélite et la phase finale 2013-2018 a été mis au point. Ce Plan prévoit l'introduction d'au moins une dose de vaccine antipoliomyélitique inactivé

immunization schedules as a strategy to mitigate the potential consequences should any re-emergence of type 2 poliovirus occur following the planned withdrawal of Sabin type 2 strains from oral polio vaccine (OPV).[1]

This position paper on polio vaccines replaces the 2014 WHO position paper, and summarizes recent developments in the field. The recommendations from the 2014 WHO position paper on the use of polio vaccine, in particular on the addition of at least one dose of IPV for countries using exclusively OPV, remain valid. This position paper reflects the global switch from trivalent to bivalent OPV scheduled to take place in April 2016. Recommendations on the use of polio vaccines have been discussed on multiple occasions by SAGE, most recently in October 2015; evidence presented at these meetings can be accessed at: http://www.who.int/immunization/sage/previous/en/index.html.

Background

Epidemiology

Poliomyelitis is an acute communicable disease caused by any of 3 poliovirus serotypes (types 1, 2 or 3). In the pre-vaccine era when poliovirus was the leading cause of permanent disability in children, almost all children became infected by polioviruses, with on average 1 in 200 susceptible individuals developing paralytic poliomyelitis.[2] Polioviruses are spread by faecal-to-oral and oral-to-oral transmission. Where sanitation is poor, faecal-to-oral transmission predominates, whereas oral-to-oral transmission may be more common where standards of sanitation are high. In most settings, mixed patterns of transmission are likely to occur.

In 1988, when the annual global burden of paralytic poliomyelitis was estimated to be >350 000 cases, with wild poliovirus (WPV) transmission reported in >125 countries,[3] the WHA resolved to eradicate poliomyelitis by the year 2000 and the Global Polio Eradication Initiative (GPEI) was established. Worldwide, sustained use of polio vaccines since 1988 has led to a precipitous drop in the global incidence of poliomyelitis by >99% and the number of countries with endemic polio from 125 to just 2 in 2015 (Afghanistan and Pakistan). Of the 359 reported cases of paralytic polio caused by wild polioviruses with onset in 2014, all were due to WPV type 1 (WVP1). In contrast, only 73 cases with onset in 2015, all due to WPV1, were reported, the lowest number for any calendar year on record. The geographic distribution of WPV transmission has been progressively reduced, with cases reported

(VPI) dans les calendriers de vaccination systématique en tant que stratégie pour atténuer les conséquences potentielles d'une éventuelle réémergence de poliovirus de type 2 après le retrait prévu des souches Sabin de type 2 du vaccin antipoliomyélitique oral (VPO).[1]

Cette note de synthèse actualisée sur les vaccins antipoliomyélitiques remplace la note précédente de l'OMS publiée en 2014 et résume les faits récents dans le domaine. Les recommandations de cette précédente note sur l'utilisation du vaccin antipoliomyélitique, en particulier concernant l'addition d'au moins une dose de VPI pour les pays qui utilisent exclusivement le VPO, restent valides. La nouvelle note de synthèse traite du passage à l'échelle mondiale du VPO trivalent au VPO bivalent prévu en avril 2016. Les recommandations relatives à l'utilisation des vaccins antipoliomyélitiques ont été discutées en de multiples occasions par le SAGE et en dernier lieu en octobre 2015; les éléments présentés lors de ces réunions peuvent être consultés à l'adresse: http://www.who.int/immunization/sage/previous/en/index.html.

Contexte

Épidémiologie

La poliomyélite est une maladie transmissible aiguë causée par l'un des 3 sérotypes de poliovirus (1, 2 ou 3). Avant l'ère des vaccins, lorsque les poliovirus représentaient la principale cause d'incapacité permanente chez les enfants, la quasi-totalité de la population infanto-juvénile était infectée par ces virus et, en moyenne, 1 individu sensible sur 200 contractait une poliomyélite paralytique.[2] Les poliovirus se propagent par transmission fécale-orale ou orale-orale. Lorsque l'assainissement est insuffisant, la transmission fécale-orale est prédominante, tandis que le mode de transmission oral-oral peut être plus courant dans les zones où les normes d'assainissement sont strictes. Dans la plupart des contextes, on rencontrera probablement un schéma de transmission mixte.

En 1988, alors que la charge annuelle mondiale de poliomyélite paralytique était estimée à plus de 350 000 cas, avec une transmission de poliovirus sauvages (PVS) signalée dans >125 pays,[3] l'Assemblée mondiale de la Santé a pris la résolution d'éradiquer la poliomyélite d'ici 2000 et l'Initiative mondiale pour l'éradication de la poliomyélite (IMEP) a été mise en place. À l'échelle de la planète, l'utilisation suivie des vaccins antipoliomyélitiques a conduit à une chute vertigineuse de l'incidence mondiale de la poliomyélite de >99% et le nombre de pays d'endémie pour cette maladie est passé de 125 à 2 seulement (Afghanistan et Pakistan). Sur les 359 cas notifiés de poliomyélite paralytique provoquée par un poliovirus sauvage apparus en 2014, la totalité était due à un PVS de type 1 (PVS1). À contrario, 73 cas seulement, tous dus à des PVS1, ont été notifiés comme apparus en 2015, soit le chiffre le plus faible enregistré jusqu'à présent pour une année calendaire. Les zones géographiques de transmission des PVS ont progressivement

[1] Polio Eradication and Endgame Strategic Plan 2013–2018. Available at http://www.polioeradication.org/resourcelibrary/strategyandwork.aspx, accessed March 2016.

[2] Bernier R. Some observations on poliomyelitis lameness surveys. Rev Infect Dis. 1984; May-Jun:6, Suppl 2:S371–375.

[3] Sutter RW et al. Poliovirus vaccine-live. In: Plotkin SA, Orenstein WA, Offit PA. Vaccines, 6th edition 2013. Philadelphia: Elsevier-Saunders, 598–645.

[1] Plan stratégique pour l'éradication de la poliomyélite et la phase finale 2013-2018. Disponible à l'adresse: http://www.polioeradication.org/Resourcelibrary/Strategyandwork.aspx, consulté en mars 2016.

[2] Bernier R. Some observations on poliomyelitis lameness surveys. Rev Infect Dis. 1984; May-Jun:6 Suppl 2:S371–375.

[3] Sutter RW et al. Poliovirus vaccine-live. In Plotkin SA, Orenstein WA, Offit PA. Vaccines, 6th edition 2013. Philadelphia: Elsevier-Saunders, 598–645.

from only 2 countries in 2015 compared to 9 countries in 2014.

The last case of poliomyelitis caused by naturally circulating WPV type 2 (WPV2) was recorded in India in 1999. Global eradication of WPV2 was certified in 2015. No case due to WPV type 3 (WPV3) has been detected globally since 10 November 2012 in Nigeria.

In the absence of cases of polio caused by WPV2 for >16 years, type 2 vaccine viruses which are components of the current live OPV have become a significant cause of paralytic polio. It is now important to eliminate this vaccine-related disease burden.

Pathogen

Polioviruses are human enteroviruses of the Picornaviridae family. Polioviruses are non-enveloped viruses with a single-stranded RNA genome and a protein capsid. The 3 serotypes of polioviruses have different antigenic sites in the capsid proteins.

Polioviruses share most of their biochemical and biophysical properties with other enteroviruses. They are resistant to inactivation by many common detergents and disinfectants, including soaps, but are rapidly inactivated by exposure to ultraviolet light. Viral infectivity is stable for months at +4 °C and for several days at +30 °C.[2]

Disease

The incubation period is commonly 7–10 days (range 4–35 days). Most people infected with poliovirus do not have symptoms; viral replication in the pharynx and gastrointestinal tract results in virus excretion in saliva and faeces. Approximately 25% of those infected develop transient minor symptoms, including fever, headache, malaise, nausea, vomiting and sore throat. In some individuals (approximately 4%) with this minor illness, signs of meningeal irritation develop, with neck stiffness, severe headache, and pain in limbs, the back and the neck, suggestive of aseptic meningitis (non-paralytic polio). This form of polio lasts between 2 and 10 days and in almost all cases recovery is complete.

Paralytic poliomyelitis is a rare outcome and occurs when poliovirus enters the central nervous system by peripheral or cranial nerve axonal flow and replicates in anterior horn cells (motor neurons) of the spinal cord. It is observed in <1% of poliovirus infections in children <5 years of age, varying with serotype and age. The ratio of paralytic cases to infections was estimated per 100 infections at approximately 0.5 for serotype 1, 0.05 for serotype 2, and 0.08 for serotype 3, based on data from 15 countries.[2] Depending on the degree and extent to which motor neurons are affected, temporary or permanent paralysis of the affected muscles may ensue. In rare cases, viral destruction of bulbar cells results in respiratory paralysis and death.

régressé, les pays notifiant des cas d'infection par ce type de virus n'étant plus que 2 en 2015, contre 9 en 2014.

Le dernier cas de poliomyélite causé par un PVS de type 2 (PVS2) naturellement circulant est apparu en Inde en 1999. L'éradication à l'échelle mondiale des PVS2 a été certifiée en 2015. Aucun cas dû à un PVS de type 3 (PVS3) n'a été détecté depuis le 10 novembre 2012 au Nigéria.

En l'absence de cas de poliomyélite causé par un PVS2 depuis >16 ans, les virus vaccinaux de type 2 entrant dans la composition du VPO vivant actuel sont devenus une cause d'ampleur significative de poliomyélite paralytique. Il est maintenant important d'éliminer la charge de morbidité liée à la vaccination.

Agent pathogène

Les poliovirus sont des entérovirus humains de la famille des Picornaviridae. Il s'agit de virus non enveloppés, avec un génome constitué d'ARN monocaténaire et une capside protéinique. Les protéines de capside des 3 sérotypes de poliovirus présentent des sites antigéniques différents.

Les poliovirus ont en commun avec d'autres entérovirus la plupart de leurs propriétés biochimiques et biophysiques. Ils résistent à l'inactivation par de nombreux détergents et désinfectants courants, y compris les savons, mais sont rapidement inactivés par une exposition à la lumière ultraviolette. L'infectiosité virale est stable pendant plusieurs mois à +4° C et pendant plusieurs jours à +30° C.[2]

Maladie

La période d'incubation est habituellement de 7 à 10 jours (plage de variation: 4-35 jours). La plupart des personnes infectées par un poliovirus ne présentent pas de symptôme, la réplication virale dans le tractus gastro-intestinal ou le pharynx entraînant l'excrétion du virus dans la salive et les selles. Environ 25% des individus infectés manifestent des symptômes mineurs et transitoires, qui peuvent être de la fièvre, des céphalées, une sensation de malaise, des nausées, des vomissements ou un mal de gorge. Chez certaines personnes présentant cette forme mineure de la maladie (approximativement 4%), des signes d'irritation méningée apparaissent, y compris une raideur de la nuque, des céphalées sévères ou des douleurs dans les membres, le dos ou la nuque, orientant vers une méningite aseptique (poliomyélite non paralytique). Cette forme de poliomyélite dure entre 2 et 10 jours et aboutit à un rétablissement complet dans presque tous les cas.

La poliomyélite paralytique est rare et se développe lorsque le poliovirus pénètre dans le système nerveux central par le flux axonal dans les nerfs périphériques ou crâniens et se réplique dans les cellules de la corne antérieure de la moelle épinière (neurones moteurs). Elle est observée chez <1% des enfants de <5 ans infectés par le poliovirus, avec des variations en fonction du sérotype et de l'âge. La proportion de cas paralytiques parmi les individus infectés par un poliovirus a été estimée, pour 100 infections à approximativement 0,5 pour le sérotype 1, à 0,05 pour le sérotype 2 et à 0,08 pour le sérotype 3, d'après des données émanant de 15 pays.[2] Selon l'intensité et l'ampleur de l'atteinte des neurones moteurs, il peut s'ensuivre une paralysie temporaire ou permanente des muscles touchés. Dans de rares cas, la destruction par le virus des cellules bulbaires entraîne une paralysie respiratoire et la mort.

The typical clinical manifestation of paralytic poliomyelitis is acute flaccid paralysis (AFP) affecting the limbs, principally the legs, usually asymmetrically, while sensation remains intact. Persistent paralysis and resulting deformities are common sequelae. The case-fatality rates among paralytic cases range from 5% to 10% in children and from 15% to 30% in adolescents and adults, predominantly associated with bulbar involvement. Post-polio syndrome, with symptoms appearing 15–30 years after recovery from the original paralytic attack, occurs in 25%–50% of cases, with symptoms including acute or increased muscular weakness, pain in the muscles, and fatigue.

Treatment

No specific anti-viral drugs are available for poliomyelitis, although some poliovirus antiviral compounds are currently being developed (see section on immunocompromised persons). Treatment consists of supportive, symptomatic care during the acute phase, including respiratory support in cases with respiratory muscle paralysis. Neuromuscular sequelae are mitigated by physiotherapy and orthopaedic treatment.

Diagnosis

The diagnosis of paralytic poliomyelitis is supported by: (i) clinical course, (ii) virological testing, and (iii) residual neurologic deficit 60 days after onset of symptoms.[1]

Laboratory testing, such as the measurement of antibodies (especially pre- and post-onset of paralysis), and other studies, such as magnetic resonance imaging, electromyography, and/or nerve conduction tests, can help strengthen or exclude the diagnosis of poliomyelitis.

WHO uses a sensitive screening case definition for the identification of AFP cases and for investigation of any case of AFP in a person younger than 15 years or in a person of any age in whom poliomyelitis is suspected. However, virological examination is essential for confirmation of the diagnosis of poliomyelitis; this involves detection of poliovirus from the stools of patients with AFP and further characterization of the isolated poliovirus to determine whether it is vaccine-associated, vaccine-derived or wild virus.[4] Molecular diagnostics such as polymerase chain reaction are used to differentiate WPV, VDPV, and Sabin-like poliovirus. In addition all discordant poliovirus isolates are partially sequenced to determine their origin and relatedness to other isolates. According to the laboratory results and review by national polio expert committees, cases are further classified as confirmed, polio-compatible, or polio-negative. The AFP surveillance is supplemented by environmental surveillance which involves testing sewage or

[4] WHO-IVB, Polio Laboratory Manual 2004. Available at http://whqlibdoc.who.int/hq/2004/WHO_IVB_04.10.pdf, accessed February 2016.

La manifestation clinique typique de la poliomyélite paralytique est la paralysie flasque aiguë (PFA) qui touche les membres, principalement les jambes, habituellement de façon asymétrique, la sensibilité restant intacte. Une paralysie persistante et les déformations qui en résultent font partie des séquelles courantes. Le taux de létalité parmi les cas de paralysie se situe entre 5 et 10% chez l'enfant et entre 15 et 30% chez l'adolescent et l'adulte, en association dans la majorité des cas avec une atteinte bulbaire. Un syndrome postpoliomyélitique, dont les symptômes se manifestent 15 à 30 jours après la guérison de l'attaque paralytique initiale, apparaît dans 25 à 50% des cas; ces symptômes incluent une faiblesse musculaire accrue ou aiguë, des douleurs musculaires et une grande fatigue.

Traitement

Aucun médicament antiviral spécifique n'est disponible contre la poliomyélite, même si certains antiviraux visant les poliovirus sont actuellement en cours de mise au point (voir le paragraphe consacré aux personnes immunodéprimées). Le traitement consiste en des soins symptomatiques et de soutien pendant la phase aiguë, y compris une assistance respiratoire dans les cas de paralysie des muscles de la respiration. Les séquelles neuromusculaires sont atténuées par la kinésithérapie et le traitement orthopédique.

Diagnostic

Le diagnostic de la poliomyélite paralytique s'appuie sur: i) l'évolution clinique, ii) les tests virologiques et iii) le déficit neurologique résiduel 60 jours après l'apparition des symptômes.[1]

Des analyses de laboratoire, comme le dosage des anticorps (en particulier avant et après l'apparition de la paralysie), ainsi que d'autres méthodes d'investigation comme l'imagerie par résonance magnétique (IRM), l'électromyographie et/ou les tests de conduction nerveuse, peuvent contribuer à renforcer ou exclure un diagnostic de poliomyélite.

Dans le cadre du dépistage de la maladie, l'OMS utilise une définition de cas sensible pour l'identification des cas de PFA et pour l'investigation de tout cas de PFA chez une personne <15 ans ou chez une personne d'âge quelconque que l'on suspecte d'être atteinte de poliomyélite. Néanmoins, l'examen virologique est essentiel pour confirmer le diagnostic de poliomyélite; il suppose la détection du poliovirus dans les selles des patients souffrant de PFA et la caractérisation plus poussée du poliovirus isolé pour déterminer s'il s'agit d'un virus associé au vaccin, dérivé de celui-ci ou sauvage.[4] Des méthodes de diagnostic moléculaires comme l'amplification génique (PCR) sont employées pour différencier les PVS, les PVDV et les poliovirus analogues d'une souche Sabin. En outre, tous les isolements de poliovirus pour lesquels les tentatives de catégorisation donnent des résultats contradictoires sont partiellement séquencés pour déterminer leur origine et leur degré de parenté avec d'autres isolements. En fonction des résultats de laboratoire et de l'examen par un comité national d'experts de la poliomyélite, les cas sont ensuite classés comme confirmés,

[4] WHO-IVB, Polio Laboratory Manual, 2004. Disponible sur http://whqlibdoc.who.int/hq/2004/WHO_IVB_04.10.pdf, consulté en février 2016.

other environmental samples for the presence of poliovirus.

Naturally-acquired immunity

Immunocompetent individuals infected by poliovirus develop immunity through humoral (circulating antibody) and mucosal (secretory immunoglobulin A) immune responses. The presence in blood of neutralizing antibody against polioviruses indicates protective immunity; detectable antibody is an excellent correlate of protection against paralytic disease.[5] However, immunity is serotype-specific with no cross-protection between serotypes. Mucosal immunity decreases the replication and excretion (shedding) of the virus, and thus provides a potential barrier to its transmission. Individuals with B-cell related immunodeficiency disorders are at increased risk for paralytic manifestations of poliomyelitis or prolonged excretion of virus.

Vaccines

IPV, first developed and licensed in 1955, is given by injection and is available only in trivalent form containing the 3 virus serotypes PV1, PV2 and PV3. OPV was initially licensed in 1961 as a monovalent (mOPV) vaccine, followed by a trivalent version (tOPV) licensed in 1963.

Bivalent OPV (bOPV containing types 1 and 3 Sabin viruses) has been licensed and used in some settings since December 2009. Following the planned global switch from tOPV to bOPV in April 2016, tOPV will no longer be available and will be replaced by bOPV. Thereafter, the only OPV containing serotype 2 will be type 2 monovalent OPV (mOPV2) stockpiled for emergency use (see below).

1. Oral poliovirus vaccine (OPV)

Vaccine characteristics

OPV is composed of live attenuated polioviruses derived of their parent WPV strains by passage in nonhuman cells to obtain the 3 vaccine strains (Sabin 1, 2, and 3). Attenuation of the virus in cell culture greatly reduces its neurovirulence and transmissibility.[6]

There have been several licensed formulations of OPV: (i) monovalent OPVs against type 1 (mOPV1), type 2 (mOPV2) or type 3 (mOPV3); (ii) bivalent OPV (bOPV) containing types1 and 3; and (iii) trivalent (tOPV) containing types 1, 2 and 3.[7]

[5] Sutter RW et al. Defining surrogate serologic tests with respect to predicting protective vaccine efficacy: Poliovirus vaccination. Williams JC, Goldenthal KL, Burns D, Lewis BP (eds), in Combined Vaccines and Simultaneous Administration: Current Issues and Perspectives. New York Academy Sciences, New York, 1995; 289–299.

[6] Sabin AB, et al. History of Sabin attenuated poliovirus oral live vaccine strains. J Biol Standardization. 1973; 1:115–118.

[7] Recommendations to assure the quality, safety and efficacy of live attenuated poliomyelitis vaccine (oral). [Replacement of: WHO Technical Report Series (TSR) 904, Annex 1 and Addendum TRS 910, Annex 1]. Geneva, World Health Organization,2012. Available at http://www.who.int/biologicals/vaccines/BS2185_OPV_Post_ECBS_DB_TZ_DBFinal12Feb2013.pdf, accessed February 2016.

compatibles avec une poliomyélite ou non poliomyélitiques. La surveillance de la PFA est complétée par une surveillance environnementale, qui consiste notamment à analyser des échantillons d'eaux usées ou d'autres prélèvements environnementaux pour rechercher la présence de poliovirus.

Immunité acquise de manière naturelle

Chez les sujets immunocompétents infectés par le poliovirus, une immunité se développe par le biais des réponses immunitaires humorale (anticorps circulants) et mucosale (immunoglobuline A sécrétoire). La présence dans le sang d'anticorps neutralisants dirigés contre les poliovirus indique l'acquisition d'une immunité protectrice; cette présence à un niveau détectable est extrêmement bien corrélée à l'existence d'une protection contre la forme paralytique de la maladie.[5] Cependant, l'immunité obtenue est spécifique d'un sérotype, sans protection croisée entre sérotypes différents. L'immunité mucosale réduit la réplication et l'excrétion du virus et fait ainsi potentiellement obstacle à sa transmission. Les individus souffrant d'un déficit immunitaire en lymphocytes B sont exposés à un risque accru de manifestations paralytiques de la poliomyélite ou d'excrétion prolongée du virus.

Vaccins

Le VPI, mis au point en premier et homologué en 1955, est administré par injection et n'est disponible que dans une formulation trivalente, contenant les 3 poliovirus sérotypés PV1, PV2 et PV3. Le VPO a été initialement homologué en 1961 en tant que vaccin monovalent (VPOm), puis dans une version trivalente (VPOt) en 1963.

Un VPO bivalent (VPOb contenant des virus Sabin de types 1 et 3) a été homologué. Il est utilisé dans certains contextes depuis décembre 2009. Après le passage planifié du VPOt au VPOb en avril 2016, le VPOt ne sera plus disponible et sera remplacé par le VPOb. Par la suite, le seul VPO renfermant le sérotype 2 sera le VPO monovalent type 2 (VPOm2), avec des stocks disponibles pour faire face aux situations d'urgence (voir plus loin).

1. Vaccin antipoliomyélitique oral (VPO)

Caractéristiques du vaccin

Le VPO contient des poliovirus atténués vivants, dérivés par passage de leurs souches parentes (PVS) dans des cellules d'origine non humaines en vue d'obtenir les 3 souches vaccinales (Sabin 1, 2 et 3). L'atténuation du virus par cultures successives réduit grandement sa neurovirulence et sa capacité de transmission.[6]

Plusieurs formulations de VPO ont été homologuées: i) une forme monovalente contre le type 1 (PVOm1), contre le type 2 (PVOm2) ou le type 3 (VPOm3); ii) une forme bivalente (VPOb) contenant les types1 et 3; et iii) une forme trivalente (VPOt) renfermant les types 1, 2 et 3.[7]

[5] Sutter RW et al. Defining surrogate serologic tests with respect to predicting protective vaccine efficacy: Poliovirus vaccination. Williams JC, Goldenthal KL, Burns D, Lewis BP (eds), in Combined Vaccines and Simultaneous Administration: Current Issues and Perspectives. New York Academy Sciences, New York, 1995; 289–299.

[6] Sabin AB, et al. History of Sabin attenuated poliovirus oral live vaccine strains. J Biol Standardization. 1973; 1:115–118.

[7] Recommendations to assure the quality, safety and efficacy of live attenuated poliomyelitis vaccine (oral). [Replacement of: WHO Technical Report Series (TRS) 904, Annex 1 and Addendum TRS 910, Annex1]. Genève: Organisation mondiale de la Santé; 2012. Disponible uniquement en langue anglaise à l'adresse suivante: http://www.who.int/biologicals/vaccines/BS2185_OPV_Post_ECBS_DB_TZ_DBFinal12Feb2013.pdf, consulté en février 2016.

The eradication of indigenous WPV2 in 1999, coupled with the continuing emergence of neurovirulent circulating type 2 vaccine-derived polioviruses (cVDPV2s) as well as vaccine-associated paralytic poliomyelitis (VAPP), led to the recommendation that there should be coordinated global cessation of use of the type 2 component of OPV and a switch from tOPV to bOPV; this was recommended by SAGE to take place in April 2016. After the switch, mOPV2, which is licensed for outbreak response using an emergency stockpile, will then be used solely for this purpose, e.g. following an emergence of cVDPV2 or WPV2.

OPV is administered as 2 drops (~0.1 mL), directly into the mouth. It is highly heat-sensitive and must be kept frozen for long-term storage or, after thawing, at temperatures between +2 °C and +8 °C for a maximum of 6 months. Vaccine vial monitors give a visual indication of whether the vaccine has been kept at the correct temperature conditions.

Safety of OPV

The only serious adverse events associated with OPV are rare cases of vaccine-associated paralytic poliomyelitis, which can occur in vaccinated individuals or their contacts, and the emergence of vaccine-derived polioviruses.[2] All available evidence indicates that OPV is non-teratogenic and safe to administer to pregnant women and HIV-infected persons. Since bOPV contains only 2 of the 3 components of tOPV, its safety profile is assumed to be better than that of tOPV, because 26%–31% of VAPP cases are caused by Sabin type 2 viruses.[8]

Vaccine-associated paralytic poliomyelitis (VAPP)

Cases of VAPP are clinically indistinguishable from poliomyelitis caused by WPV. Given the complexities of VAPP diagnosis and classification,[9] additional follow-up and review by a national expert classification committee is necessary, and consequently there are limited data on VAPP incidence from developing countries. The incidence of VAPP has been estimated at 2–4 cases/million birth cohort per year in countries using OPV.[8]

Available data suggest differences in the epidemiology of VAPP in developing and industrialized countries. In the latter, VAPP occurs mainly in early infancy associated with the first dose of OPV and decreases sharply (>10 fold) with subsequent OPV doses. In lower-income countries, which experience relatively lower rates of vaccine seroconversion, this decline is more gradual and VAPP may occur with second or subsequent doses of OPV, with the age distribution concentrated among children aged 1–4 years, as demonstrated by data from

L'éradication des PVS2 autochtones en 1999, ainsi que l'émergence en continu de poliovirus circulants dérivés d'une souche vaccinale de type 2 neurovirulants (PVDV2c) et de poliomyélites paralytiques associées au vaccin (PPAV), ont amené l'OMS à recommander la cessation coordonnée à l'échelle mondiale de l'utilisation de la composante du VPO dirigée contre le type 2 et le passage du VPOt au VPOb, dont le SAGE a préconisé qu'il s'effectue en avril 2016. Après cette transition, le VPOm2, homologué pour répondre à une éventuelle flambée à l'aide d'un stock d'urgence, sera par la suite destiné uniquement à cette fin, par exemple suite à l'émergence de PVDV2c ou de PVS2.

Le VPO s'administre en introduisant 2 gouttes (~0,1 ml) directement dans la bouche. C'est un vaccin très sensible à la chaleur, qui doit être conservé à l'état congelé pour un stockage de longue durée ou après décongélation, à une température comprise entre 2 °C et +8 °C pendant 6 mois au maximum. La pastille de contrôle placée sur les flacons de vaccin donne une indication visuelle du respect des conditions de température pendant la conservation.

Innocuité du VPO

Les seules manifestations indésirables graves associées au VPO sont les cas rares de poliomyélite paralytique associés à la vaccination, qui peuvent apparaître chez des individus vaccinés ou leurs contacts, et l'émergence de poliovirus dérivés d'une souche vaccinale.[2] Tous les éléments disponibles indiquent que le VPO n'est pas tératogène et peut être administré sans risque aux femmes enceintes et aux personnes infectées par le VIH. Le VPOb ne renfermant que 2 des 3 composantes du VPOt, on suppose que son profil d'innocuité est meilleur que celui du VPOt, car 26 à 31% des cas de PPAV sont causés par des virus Sabin de type 2.[8]

Poliomyélite paralytique associée à la vaccination (PPAV)

Les cas de PPAV sont cliniquement impossibles à distinguer d'une poliomyélite causée par un PVS. Compte tenu de la complexité du diagnostic des PPAV et de leur classification,[9] un suivi et un examen complémentaires par un comité national d'experts de la classification sont nécessaires et on dispose donc de peu de données sur l'incidence des PPAV en provenance des pays en développement. Cette incidence a été estimée à 2-4 cas/million d'individus d'une cohorte de naissance et par an dans les pays utilisant le VPO.[8]

Les données disponibles suggèrent l'existence de différences dans l'épidémiologie des PPAV entre les pays en développement et les pays industrialisés. Dans ces derniers, la PPAV apparaît principalement pendant la petite enfance, en association avec la première dose de VPO et diminue très fortement (d'un facteur supérieur à 10) avec les doses de VPO suivantes. Dans les pays disposant de moindres revenus, où les taux de séroconversion avec le vaccin sont relativement plus bas, cette diminution est plus progressive et une PPAV peut se déclarer avec la deuxième dose de VPO ou les suivantes, la distribution de la

[8] Platt LR et al. Vaccine-associated paralytic poliomyelitis: a review of the epidemiology and estimation of the global burden. J Infect Dis. 2014;210 suppl 1:S380–9.

[9] Sutter RW et al. A new epidemiologic and laboratory classification system for paralytic poliomyelitis cases. Am Public Health. 1989; 79:495–498.

[8] Platt LR et al. Vaccine-associated paralytic poliomyelitis: a review of the epidemiology and estimation of the global burden. J Infect Dis. 2014;210 suppl 1:S380–9.

[9] Sutter RW et al. A new epidemiologic and laboratory classification system for paralytic poliomyelitis cases. Am Public Health. 1989; 79:495–498.

India[10] and Iran.[11] The main factors contributing to this difference are believed to be lower immune responsiveness to OPV and higher prevalence of maternally-derived antibody in populations in low-income settings. The introduction of one dose of IPV prior to vaccination with OPV led to the elimination of VAPP in Hungary.[12]

Vaccine-derived polioviruses (VDPVs)

The attenuated viruses in live OPV vaccines (Sabin viruses) may, through prolonged replication in an individual or in a community, re-acquire the neurovirulence and transmissibility characteristics of WPV. They may then become cVDPVs that cause isolated cases or outbreaks of paralytic poliomyelitis.[13, 14, 15] During 2011–2015, almost 90% of reported cVDPV cases (204/230) were associated with the type 2 component of tOPV.

VDPVs are genetically divergent forms of the original Sabin vaccine virus conventionally defined by >1% genetic divergence (or >10 nucleotide [nt] changes) for PV1 and PV3 and >0.6% (or >6 nt changes) for PV2. These viruses are further subdivided into 3 categories: (1) cVDPVs, when evidence of person-to-person transmission in the community exists; (2) immunodeficiency-associated VDPVs (iVDPVs), which are isolated from some people with primary B-cell or combined immunodeficiency disorders (with defects in antibody production) who may have prolonged VDPV infections (in individual cases excretion has been reported to persist for 10 years or more[16, 17]); and (3) ambiguous VDPVs (aVDPVs), which are either clinical isolates from persons with no known immunodeficiency, or sewage isolates of unknown origin.[14]

The term 'persistent cVDPV' refers to cVDPVs that continue to circulate for >6 months following detection. Persistent cVDPVs represent programmatic failures to contain the cVDPV outbreak within 6 months of detection.

In July 2015, the GPEI revised the definition of cVDPV to enhance its sensitivity.[18] In the new guidelines

maladie en fonction de l'âge étant centrée sur la tranche d'âge 1-4 ans, comme le montrent des données provenant d'Inde[10] et d'Iran.[11] On pense que les principaux facteurs contribuant à cette différence sont la plus faible réactivité immunitaire au VPO et la plus forte prévalence des anticorps d'origine maternelle dans les populations des zones à faible revenu. L'introduction d'une dose de VPI avant la vaccination par le VPO a abouti à l'élimination de la PPAV en Hongrie.[12]

Poliovirus dérivés d'une souche vaccinale (PVDV)

Les virus atténués présents dans les vaccins VPO vivants (virus Sabin) peuvent, à l'issue d'une réplication prolongée chez un individu ou dans une collectivité, réacquérir les caractéristiques de neurovirulence et de transmissibilité des PVS. Ils peuvent devenir des PVDVc, à l'origine de cas isolés ou de flambées de poliomyélite paralytique.[13, 14, 15] Au cours de la période 2011-2015, près de 90% des cas de PVDVc notifiés (204/230) étaient associés à la composante de type 2 du VPOt.

Les PVDV sont des formes génétiquement divergentes du virus vaccinal Sabin original, définies par convention comme présentant un taux de divergence génétique >1% (ou >10 modifications nucléotidiques [nt]) pour le PV1 et le PV3 et >0,6% (ou >6 modifications nt) pour le PV2. Ces virus se subdivisent ensuite en 3 catégories: 1) les PVDVc lorsqu'il existe des preuves d'une transmission interhumaine dans la collectivité; 2) les PVDV associés à une immunodéficience (PVDVi), qui sont isolés chez certaines personnes souffrant d'un déficit primaire en lymphocytes B ou d'immunodéficience combinée (chez lesquelles la production d'anticorps est déficiente) présentant des infections prolongées par des PVDV (dans certains cas, une excrétion persistant sur 10 ans ou plus a été rapportée[16, 17]) et 3) les PVDV ambigus (PVDVa), que l'on trouve dans des isolements cliniques provenant d'individus sans déficit immunitaire connu ou dans des isolements effectués sur des eaux usées d'origine inconnue.[14]

On désigne par le terme «PVDVc persistants» des PVDVc qui continuent de circuler pendant >6 mois après leur détection. Les PVDVc persistants représentent des échecs programmatiques pour endiguer la flambée de PVDVc dans les 6 mois suivant sa détection.

En juillet 2015, l'IMEP a révisé la définition d'un PVDVc en renforçant sa sensibilité.[18] Dans les nouvelles lignes directrices,

[10] Kohler KA et al. Vaccine-associated paralytic poliomyelitis in India during 1999: decreased risk despite massive use of oral polio vaccine. Bull World Health Organ. 2002; 80(3):210–216.

[11] Considerations for the timing of a single dose of IPV in the routine immunization schedule http://www.who.int/immunization/sage/meetings/2013/november/1_Sutter_IPV_age_tech_background_14_October_2013_final.pdf, accessed February 2016.

[12] Dömök I. Experiences associated with the use of live poliovirus vaccine in Hungary,1959–1982. Rev Inf Dis. 1984; 6(Suppl. 2):S413–S418.

[13] Estívariz CF et al. A large vaccine-derived poliovirus outbreak on Madura Island–Indonesia. J Inf Dis. 2005; 197:347–354.

[14] Jenkins HE et al. Implications of a circulating vaccine-derived poliovirus in Nigeria for polio eradication. N Eng J Med. 2010; 362:2360–2369.

[15] Duintjer Tebbens RJ et al. Oral poliovirus vaccine evolution and insights relevant to modeling the risks of circulating vaccine-derived polioviruses (cVDPVs). Risk Anal 2013;23(4):680–702.

[16] See No. 42, 2006, pp. 398–404.

[17] Duintjer Tebbens RJ et al. Modeling the prevalence of immunodeficiency-associated long-term vaccine-derived poliovirus excretors and the potential benefits of antiviral drugs. BMC Infect Dis 2015;15(379):doi:10.1186/s12879-015-1115-5.

[18] Global Polio Eradication Initiative (2015). Reporting and classification of vaccine-derived polioviruses. Available at http://www.polioeradication.org/Portals/0/Document/Resources/VDPV_ReportingClassification.pdf, accessed February 2016.

[10] Kohler KA et al. Vaccine-associated paralytic poliomyelitis in India during 1999: decreased risk despite massive use of oral polio vaccine. Bull World Health Organ. 2002; 80(3):210–216.

[11] Considerations for the timing of a single dose of IPV in the routine immunization schedule http://www.who.int/immunization/sage/meetings/2013/november/1_Sutter_IPV_age_tech_background_14_October_2013_final.pdf , consulté en février 2016.

[12] Dömök I. Experiences associated with the use of live poliovirus vaccine in Hungary,1959–1982. Rev Inf Dis. 1984; 6(Suppl. 2):S413–S418.

[13] Estívariz CF et al. A large vaccine-derived poliovirus outbreak on Madura Island–Indonesia. J Inf Dis. 2005; 197:347–354.

[14] Jenkins HE et al. Implications of a circulating vaccine-derived poliovirus in Nigeria for polio eradication. N Eng J Med. 2010; 362:2360-2369.

[15] Duintjer Tebbens RJ et al. Oral poliovirus vaccine evolution and insights relevant to modeling the risks of circulating vaccine-derived polioviruses (cVDPVs). Risk Anal 2013;23(4):680-702.

[16] Voir N° 42, 2006, pp. 398-404.

[17] Duintjer Tebbens RJ et al. Modeling the prevalence of immunodeficiency-associated long-term vaccine-derived poliovirus excretors and the potential benefits of antiviral drugs. BMC Infect Dis 2015;15(379):doi:10.1186/s12879-015-1115-5.

[18] Global Polio Eradication Initiative (2015). Reporting and classification of vaccine-derived polioviruses. Disponible sur http://www.polioeradication.org/Portals/0/Document/Resources/VDPV_ReportingClassification.pdf, consulté en février 2016.

cVDPVs are defined as genetically linked VDPVs isolated from: (i) at least 2 individuals – not necessarily AFP cases – who are not household contacts; (ii) one individual and one or more environmental surveillance (ES) samples; or (iii) at least 2 ES samples if they were collected at more than one distinct ES collection site (no overlapping of catchment areas), or from one site if collection was more than 2 months apart, or a single VDPV isolate with genetic features indicating prolonged circulation (i.e. a number of nt changes from parent Sabin strains suggesting ≥1.5 years of circulation, or 15 nt changes).

The epidemiological characteristics of cVDPVs are similar or identical to those of WPVs; they cause similar paralytic disease and have capacity for sustained person-to-person transmission. They have lost the original attenuating mutations, can replicate at 39.5 °C, and are usually recombinants with other species of enterovirus. cVDPVs were first recognized in 2000 during an outbreak in Hispaniola.[19] Recent experience indicates that low vaccination coverage is a major risk factor for cVDPV outbreaks, that cVDPVs have the ability to continue circulating for prolonged periods, as seen in Nigeria and Pakistan, and that cVDPVs can be imported and spread in any under-vaccinated community in a developed country, as occurred in the Amish community, USA.[20]

In 2014, a total of 56 cases of paralytic poliomyelitis caused by cVDPVs were reported from 5 countries; in 55 of the cases the virus was serotype 2 and in one it was serotype 1. Nigeria reported the largest number of cases (*n*=30).[21] In 2015, as of 15 December, 7 countries reported a total of 24 cases of paralytic poliomyelitis caused by cVDPVs, most of which were serotype 1 (*n*=17). These cases occurred in Madagascar (*n*=10), Lao People's Democratic Republic (*n*=5), Guinea, Myanmar, Ukraine and Pakistan (*n*=2 each) and Nigeria (*n*=1).

Immunogenicity and effectiveness

The effectiveness of OPV in controlling poliomyelitis and eliminating the circulation of wild polioviruses is amply demonstrated by the sharp decline in the incidence of poliomyelitis following the introduction of OPV in both industrialized and developing countries.[22] Until now tOPV has been the vaccine of choice for the GPEI and its use was largely responsible for the progress towards eradication, including the eradication of WPV2 globally in 1999.

les PVDVc sont définis comme: des PVDV génétiquement liés isolés: 1) chez au moins 2 individus – non nécessairement des cas de PFA – qui ne sont pas des contacts domestiques, 2) chez un individu et dans un ou plusieurs échantillons fournis par la surveillance environnementale, ou 3) dans au moins 2 échantillons environnementaux s'ils ont été recueillis dans plus d'un site de collecte pour la surveillance environnementale distincts (sans recouvrement des zones de captage), ou encore dans un seul site si les échantillons ont été recueillis à plus de 2 mois d'intervalle, ou bien comme un isolement unique de PVDV, présentant des caractéristiques génétiques qui indiquent une circulation prolongée (c'est-à-dire un nombre de modifications nt par rapport aux souches Sabin parentes laissant supposer une circulation pendant ≥1,5 ans, ou 15 modifications nt).

Les caractéristiques épidémiologiques des PVDVc sont analogues ou identiques à celles des PVS: ils causent une maladie paralytique similaire et sont capables d'une transmission interhumaine soutenue. Ils ont perdu leurs mutations d'atténuation de départ, peuvent se répliquer à 39,5 °C et sont habituellement susceptibles de se recombiner avec d'autres espèces d'entérovirus. Les PVDVc ont été reconnus pour la première fois en 2000, lors d'une flambée survenue à Hispaniola.[19] L'expérience récente indique qu'une faible couverture vaccinale représente un facteur de risque majeur pour l'apparition de flambées de PVDVc, que les PVDVc ont la capacité de circuler sur des périodes prolongées, comme on l'a observé au Nigéria et au Pakistan, et qu'ils peuvent être importés et propagés dans toute collectivité sous-vaccinée d'un pays développé, comme cela s'est produit pour la Communauté Amish aux États-Unis d'Amérique.[20]

En 2014, 56 cas au total de poliomyélite paralytique causée par un PVDVc ont été notifiés par 5 pays, dans 55 de ces cas, le virus appartenait au sérotype 2 et dans un autre, au sérotype 1. C'est au Nigéria que le plus grand nombre de cas (*n*=30) a été signalé.[21] Au 15 décembre 2015, 7 pays avaient notifié au total 24 cas de poliomyélite paralytique provoquée par un PVDVc, appartenant dans la plupart des cas au sérotype (*n*=17). Ces cas sont apparus à Madagascar (*n*=10), en République démocratique populaire lao (*n*=5), en Guinée, au Myanmar, en Ukraine et au Pakistan (*n*=2 chaque fois) ainsi qu'au Nigéria (*n*=1).

Immunogénicité et efficacité

L'efficacité du VPO dans l'endiguement de la poliomyélite et dans l'élimination des poliovirus sauvages circulants est amplement démontrée par la baisse radicale de l'incidence de la poliomyélite suite à l'introduction de ce vaccin dans les pays industrialisés et en développement.[22] Jusqu'à ce jour, le VPOt a représenté le vaccin de choix pour l'IMEP et son utilisation a été responsable, pour une très grande part, des progrès réalisés vers l'éradication, y compris l'éradication des PVS2 à l'échelle mondiale en 1999.

[19] Kew OM et al. Outbreak of poliomyelitis in Hispaniola associated with circulating type 1 vaccine–derived poliovirus. Science. 2002; 296:356–359.

[20] Alexander JP et al. Transmission of imported vaccine-derived poliovirus in an under-vaccinated community: Minnesota , USA. J Inf Dis. 2009; 391–397.

[21] Circulating vaccine-derived poliovirus (cVDPV) 2000–2013. Available at http://www.polioeradication.org/Dataandmonitoring/Poliothisweek/Circulatingvaccine-derivedpoliovirus.aspx, accessed February 2016.

[22] Grading of scientific evidence – table I: Efficacy/effectiveness of OPV. Available at http://www.who.int/immunization/polio_grad_opv_effectiveness.pdf, accessed February 2016.

[19] Kew OM et al. Outbreak of poliomyelitis in Hispaniola associated with circulating type 1 vaccine–derived poliovirus. Science. 2002; 296:356–359.

[20] Alexander JP et al. Transmission of imported vaccine-derived poliovirus in an under-vaccinated community: Minnesota , USA. J Inf Dis. 2009; 391–397.

[21] Circulating vaccine-derived poliovirus (cVDPV) 2000–2013. Disponible sur http://www.polioeradication.org/Dataandmonitoring/Poliothisweek/Circulatingvaccinederivedpoliovirus.aspx, consulté en février 2016.

[22] Cotation des preuves scientifiques – tableau I. Efficacy/effectiveness of OPV. Disponible uniquement en langue anglaise sur http://www.who.int/immunization/polio_grad_opv_effectiveness.pdf, consulté en février 2016.

During the first 4–6 weeks following OPV vaccination, the vast majority of non-immune vaccine recipients shed Sabin poliovirus in nasopharyngeal secretions and faeces. In unvaccinated populations, these vaccine viruses are easily transmitted within and to a lesser degree outside households, thereby vaccinating and inducing immunity in persons not reached directly by immunization programmes. In addition, such transmission may boost intestinal immunity in some persons and help to increase community protection if virulent viruses are introduced.

While non-immune vaccine recipients shed Sabin poliovirus after initial OPV vaccination, shedding is significantly reduced when subsequent vaccine doses are administered to individuals who had previously received OPV.[23]

In high-income countries, seroconversion rates in children following administration of 3 doses of tOPV approach 100% for all 3 poliovirus types.[24, 25] In large case-controlled studies in Taiwan[26] and Oman[27] the field-effectiveness of the 3-dose tOPV schedule was estimated to be >90%. However, in some developing countries, the same 3-dose course of tOPV in children was found to induce detectable antibodies in only 73% (range, 36%–99%), 90% (range 77%–100%) and 70% (range, 40%–99%) to poliovirus type 1, 2 and 3, respectively.[28] In lower-income settings, the response to OPV appears to vary, e.g. in Northern India seroconversion rates were relatively low,[29, 30] whereas in Thailand[31] and Indonesia[32] the rates were high.

The reduced antibody response to OPV in children in some low-income settings probably results from complex interactions between the host (e.g. levels of maternal antibody, poor intestinal immunity in malnourished children, diarrhoea at the time of vaccination, and household exposure to other OPV recipients), the vaccine and its delivery, and the environment (e.g. prevalence of other enteric infectious agents). In

Pendant les 4 à 6 premières semaines suivant la vaccination, la grande majorité des personnes qui étaient non immunisées lorsqu'elles avaient reçu le vaccin excrètent le poliovirus Sabin dans leurs sécrétions nasopharyngées et leurs selles. Parmi les populations non vaccinées, ces virus vaccinaux se transmettent facilement au sein des foyers et dans une moindre mesure à l'extérieur, en provoquant une vaccination ou en induisant une immunité chez des personnes non touchées directement par les programmes de vaccination. En outre, une telle transmission peut renforcer l'immunité intestinale chez certains individus et contribuer à accroître la protection collective en cas d'introduction de virus virulents.

Si les personnes non immunisées recevant le vaccin excrètent des poliovirus Sabin après une vaccination initiale avec le VPO, cette excrétion diminue significativement lorsqu'ils reçoivent les doses vaccinales ultérieures.[23]

Dans les pays à revenu élevé, les taux de séroconversion des enfants après l'administration de 3 doses de VPOt approchent les 100% pour les 3 types de poliovirus.[24,25] Dans le cadre d'études contrôlées de grande ampleur menées à Taïwan[26] et Oman,[27] l'efficacité sur le terrain du calendrier d'administration en 3 doses de VPOt a été estimée comme >90%. Cependant, dans certains pays en développement, on a constaté que le même déroulement en 3 doses de la vaccination par le VPOt n'induisait une réponse en anticorps détectable contre les poliovirus de types 1, 2 et 3 que chez 73% (plage de variation: 36-99%), 90% (plage de variation: 77-100%) et 70% (plage de variation: 40-99%) respectivement des enfants.[28] Dans les pays à faible revenu, la réponse au VPO semble variable: dans le nord de l'Inde, par exemple, les taux de séroconversion observés étaient relativement bas,[29, 30] tandis qu'en Thaïlande[31] et en Indonésie,[32] ils étaient élevés.

La diminution de la réponse en anticorps des enfants au VPO dans certains pays à faible revenu résulte probablement d'interactions complexes entre l'hôte (concentrations d'anticorps maternels, immunité intestinale insuffisante chez les enfants mal nourris, diarrhée au moment de la vaccination ou exposition au sein du foyer à d'autres personnes ayant reçu le VPO, par exemple), le vaccin et sa délivrance, et l'environnement (prévalence d'autres agents entériques infectieux, par exemple).

[23] Hird TR et al. Systematic review of mucosal immunity induced by oral and inactivated poliovirus vaccines against virus shedding following oral poliovirus vaccine challenge. PLoS Pathogens. 2012; 8(4)e1002599.

[24] Bar-On ES et al. Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and *Haemophilus influenzae* b (HIB). Cochrane Database Systematic Review. 2012 (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005530.pub3/pdf/standard, accessed February 2016).

[25] McBean AM et al. Serologic response to oral polio vaccine and enhanced potency inactivated polio vaccines. Am J Epidem. 1988; 128:615–628.

[26] Kim–Farley RJ et al Outbreak of paralytic poliomyelitis, Taiwan. Lancet. 1984; 2:1322–1324.

[27] Sutter RW et al. Outbreak of paralytic poliomyelitis in Oman: evidence for widespread transmission among fully vaccinated children. Lancet. 1991; 338:715–720.

[28] Patriarca PA. Factors affecting the immunogenicity of OPV in developing countries: a review. Rev Inf Dis. 1991; Sep-Oct; 13(5):926–939.

[29] Estívariz CF et al. Immunogenicity of poliovirus vaccines administered at age 6-9 months in Moradabad District, India: A randomized controlled phase 3 trial. Lancet Inf Dis. 2012; 12:128–135.

[30] Grassly NC et al. Protective efficacy of a monovalent oral type 1 poliovirus vaccine. Lancet. 2007; 369:1356–1362.

[31] WHO Collaborative Study Group on Oral and Inactivated Poliovirus Vaccines: Combined immunization of infants with oral and inactivated poliovirus vaccines: Results of a randomized trial in the Gambia, Oman, and Thailand. Bull World Health Organ. 1996; 74:253–268.

[32] See No. 5, 2008, pp. 45–48.

[23] Hird TR et al. Systematic review of mucosal immunity induced by oral and inactivated poliovirus vaccines against virus shedding following oral poliovirus vaccine challenge. PLoS Pathogens. 2012; 8(4)e1002599.

[24] Bar-On ES et al. Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and *Haemophilus influenzae* b (HIB). Cochrane Database Systematic Review. 2012 (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005530.pub3/pdf/standard, consulté en février 2016).

[25] McBean AM et al. Serologic response to oral polio vaccine and enhanced potency inactivated polio vaccines. Am J Epidem. 1988; 128:615–628.

[26] Kim–Farley RJ et al Outbreak of paralytic poliomyelitis, Taiwan. Lancet. 1984; 2:1322–1324.

[27] Sutter RW et al. Outbreak of paralytic poliomyelitis in Oman: evidence for widespread transmission among fully vaccinated children. Lancet. 1991; 338:715–720.

[28] Patriarca PA. Factors affecting the immunogenicity of OPV in developing countries: a review. Rev Inf Dis. 1991; Sep-Oct; 13(5):926–939.

[29] Estívariz CF et al. Immunogenicity of poliovirus vaccines administered at age 6-9 months in Moradabad District, India: A randomized controlled phase 3 trial. Lancet Inf Dis. 2012; 12:128–135.

[30] Grassly NC et al. Protective efficacy of a monovalent oral type 1 poliovirus vaccine. Lancet. 2007; 369:1356–1362.

[31] WHO Collaborative Study Group on Oral and Inactivated Poliovirus Vaccines: Combined immunization of infants with oral and inactivated poliovirus vaccines: Results of a randomized trial in the Gambia, Oman, and Thailand. Bull World Health Organ. 1996; 74:253–268.

[32] Voir N° 5, 2008, pp. 45-48.

these settings, type 2 vaccine virus interferes with immunological responses to vaccine virus types 1 and 3; consequently type 2 virus induces seroconversion preferentially, and children require multiple doses of OPV in order to respond to all 3 serotypes. A clinical trial evaluating the immunogenicity of different OPV formulations – mOPV1, mOPV3, and bOPV – compared to tOPV in an Indian population found that seroconversion rates to poliovirus types 1 and 3 following immunization with bOPV were significantly higher than those induced by tOPV.[33] Cumulative 2-dose seroconversion for poliovirus type 1 was 90% for mOPV1 and 86% for bOPV compared with 63% for tOPV, and for type 3 it was 84% for mOPV3 and 74% for bOPV compared with 52% for tOPV.[34]

A dose of OPV administered at birth, or as soon as possible after birth, can significantly improve the seroconversion rates to the types of polioviruses contained in the vaccine after subsequent doses in some settings, and induce mucosal protection before enteric pathogens can interfere with the immune response.[35, 36] Theoretically, giving the first OPV dose at a time when the infant is still protected by maternally-derived antibodies may also prevent VAPP.

Although data on birth dose seroconversion to OPV rates show great variability – from low rates in India (around 10%–15%), median rates in Egypt (32%), to high rates in South Africa (76%) – data from Brazil, China, Ghana, and India demonstrate that, in general, the birth dose increases the levels of poliovirus neutralizing antibodies and seroconversion rates achieved after completion of the routine vaccination schedule.[37, 38] A systematic review of reports published between 1959 and 2011 on seroconversion rates in infants 4–8 weeks after a single birth dose (given ≤7 days after birth) found that: (i) for tOPV the proportion of infants who seroconverted at 8 weeks was in the range 6%–42% (median: 25%) for poliovirus type 1, 2%–63% (median: 38%) for type 2, and 1%–35% (median: 15%) for type 3; (ii) for mOPV1, the seroconversion range was 10%–76% (median: 31%); (iii) for mOPV3, the range was 12%–58% (median: 35%); and (iv) for the only study on bOPV, the seroconversion rate was 20% for type 1 and 7% for type 3.[39]

Dans de tels contextes, le virus vaccinal de type 2 interfère avec les réponses immunologiques aux virus vaccinaux de types 1 et 3; en conséquence, le type 2 induit préférentiellement une séroconversion et les enfants doivent recevoir de multiples doses de VPO pour répondre à l'ensemble des 3 sérotypes. Un essai clinique évaluant l'immunogénicité de différentes formulations de VPO (VPOm1, VPOm2 et VPOb) par rapport à celle du VPOt dans une population indienne a constaté que les taux de séroconversion contre les poliovirus de types 1 et 3 après la vaccination par le VPOb étaient significativement plus élevés que ceux induits par le VPOt.[33] Après 2 doses cumulées, la séroconversion contre le poliovirus de type 1 était de 90% avec le VPOm1 et de 86% avec le VPOb, à comparer au taux de 63% obtenu avec le VPOt et contre le poliovirus de type 3, elle était de 84% avec le VPOm3 et de 74% avec le VPOb, à comparer à la valeur de 52% obtenue avec le VPOt.[34]

Une dose de VPO administrée à la naissance ou dès que possible après celle-ci, peut notablement améliorer les taux de séroconversion contre les types de poliovirus contenus dans le vaccin après administration des doses ultérieures dans certains contextes, et induire une protection mucosale avant que des agents pathogènes entériques ne puissent interférer avec la réponse immunitaire.[35,36] Théoriquement, administrer la première dose de VPO lorsque le nourrisson est encore protégé par des anticorps d'origine maternelle peut aussi prévenir la PPAV.

Bien que les données sur la séroconversion en réponse à la dose de naissance de VPO puissent présenter une grande variabilité – avec des taux bas en Inde (environ 10-15%), des taux moyens en Égypte (32%) et des taux élevés en Afrique du Sud (76%) – les données émanant du Brésil, de la Chine, du Ghana et de l'Inde montrent qu'en général la dose à la naissance accroît les concentrations d'anticorps neutralisants dirigés contre les poliovirus et les taux de séroconversion obtenus après achèvement du calendrier de vaccination systématique.[37, 38] Une revue systématique des rapports publiés entre 1959 et 2011 sur les taux de séroconversion chez les nourrissons de 4-8 semaines après une dose unique à la naissance (administrée 7 jours ou moins après la naissance) a relevé que: 1) pour le VPOt, le pourcentage de nouveau-nés séroconvertis à 8 semaines se situait dans la plage 6-42% (valeur médiane: 25%) pour le poliovirus de type 1, dans la plage 2-63% (valeur médiane: 38%) pour le type 2, et dans la plage 1-35% (valeur médiane: 15%) pour le type 3; 2) que pour le VPOm1, ce pourcentage était compris dans la plage 10-76% (valeur médiane: 31%); 3) que pour le VPOm3, il se trouvait dans la plage 12-58% (valeur médiane: 35%); et 4) que pour l'unique étude sur le VPOb, le taux de séroconversion était de 20% pour le type 1 et de 7% pour le type 3.[39]

[33] Sutter RW et al. Immunogenicity of bivalent types 1 and 3 oral poliovirus vaccine: a randomised, double-blind, controlled trial. Lancet. 2010; 376 (9753):1682–1688.

[34] John TJ. Immunisation against polioviruses in developing countries. Rev Med Virol. 1993; 3:149–160.

[35] Bhaskaram P et al. Systemic and mucosal immune response to polio vaccination with additional dose in newborn period. J Trop Paediatrics. 1997; 43(4): 232–234.

[36] Grading of scientific evidence – table II: Birth dose of OPV. Available at http://www.who.int/immunization/polio_grad_opv_birth_dose.pdf, accessed February 2016.

[37] De-Xiang D et al. Immunization of neonates with trivalent oral poliomyelitis vaccine (Sabin). Bull World Health Organ. 1986; 64(6):853–860.

[38] John TJ et al. Monovalent type 1 oral poliovirus vaccine among infants in India: report of two randomized double-blind controlled clinical trials. Vaccine. 2011 Aug 5;29(34):5793–5801

[39] Mateen FJ et al. Oral and inactivated poliovirus vaccines in the newborn: a review. Vaccine. 2013; 31(21):2517–2524.

[33] Sutter RW et al. Immunogenicity of bivalent types 1 and 3 oral poliovirus vaccine: a randomised, double-blind, controlled trial. Lancet. 2010; 376 (9753):1682–1688.

[34] John TJ. Immunisation against polioviruses in developing countries. Rev Med Virol. 1993; 3:149–160.

[35] Bhaskaram P et al. Systemic and mucosal immune response to polio vaccination with additional dose in newborn period. J Trop Paediatrics. 1997; 43(4): 232–234.

[36] Cotation des preuves scientifiques – tableau II. Birth dose of OPV. Disponible uniquement en langue anglaise sur http://www.who.int/immunization/polio_grad_opv_birth_dose.pdf, consulté en février 2016.

[37] De-Xiang D et al. Immunization of neonates with trivalent oral poliomyelitis vaccine (Sabin). Bull World Health Organ. 1986; 64(6):853–860.

[38] John TJ et al. Monovalent type 1 oral poliovirus vaccine among infants in India: report of two randomized double-blind controlled clinical trials. Vaccine. 2011 Aug 5;29(34):5793–5801

[39] Mateen FJ et al. Oral and inactivated poliovirus vaccines in the newborn: a review. Vaccine. 2013; 31(21):2517–2524.

Duration of protection

There is no evidence that protective immunity against paralytic disease wanes over time. After induction of active immunity either by vaccination or exposure to poliovirus, usually measured by circulating antibody titre, protection is life-long. However, as antibody titres decline over time and may fall below detectable levels, seroprevalence may not reflect the true immune status of a given population. While seroconversion is a reliable correlate of immunity against paralytic disease, there is no evidence that loss of detectable antibody puts immunocompetent individuals at risk for paralytic disease.

In Sri Lanka, a cross-sectional community-based survey was carried out in 3 districts (Colombo, Badulla, and Killinochi) in 2014. All 4 age groups tested (9–11 months, 3–4 years, 7–9 years, and 15 years) demonstrated high seroprevalence levels. In the 15-year age group, the seropositivity rates were 97%, 100% and 75% for type 1, 2 and 3, respectively.[40] In this study and others, type 3 seroprevalence declined with increasing age, since type 3 antibody titres are lower and fall below detectable levels earlier than titres for types 1 and 2.

In Gambia, following routine vaccination, slightly declining antibody concentrations against type 1 were found in children aged 8–9 years compared with children aged 3–4 years, but in these age groups the percentages of children with detectable antibody were almost identical (88% and 89%, respectively). Fewer children aged 8–9 years than those aged 3–4 years had antibodies against type 3 (78% versus 89%, p<0.001). Among 67 children who had received only 2 doses of tOPV, >80% retained neutralizing antibodies when tested after 5 years.[41, 42] Given the limited time since first use of bOPV in 2009, no long-term data on the persistence of antibody conferred by this vaccine are available. The higher initial immunogenicity of bOPV compared to tOPV for types 1 and 3 suggests that the persistence of antibody following vaccination with bOPV should be non-inferior or superior to that following tOPV.

Co-administration with other vaccines

OPV is usually administered concurrently with other vaccines including Bacillus Calmette-Guérin (BCG), diphtheria- pertussis- tetanus (DPT), hepatitis B, measles, *Haemophilus influenzae* type b (Hib), pneumococcal conjugate and/or rotavirus vaccines. No interference with regard to effectiveness or increased incidence

[40] Gamage D et al. Achieving high seroprevalence against polioviruses in Sri Lanka-Results from a serological survey, 2014. J Epidemiol Glob Health. 2015 Dec;5(4 Suppl 1):S67–71

[41] Nishio O et al. The trend of acquired immunity with live poliovirus vaccine and the effect of revaccination: follow up of vaccinees for ten years. J Biol Standardization. 1984; 12(1):1–10.

[42] Grading of scientific evidence – table III: Antibody persistence. Available at http://www.who.int/entity/immunization/polio_grad_duration_protection.pdf, accessed February 2016.

Durée de la protection

Il n'existe pas de preuve que l'immunité protectrice acquise contre la poliomyélitique paralytique disparaisse au cours du temps. Après l'induction d'une immunité active par vaccination ou exposition à des poliovirus, habituellement mesurée par le titre d'anticorps circulants, la protection conférée s'exerce la vie durant. Néanmoins, comme ces titres diminuent avec le temps et deviennent parfois indétectables, la séroprévalence peut ne pas refléter le statut immunitaire vrai d'une population donnée. Si la séroconversion est un corrélat fiable de l'immunité contre la poliomyélite paralytique, il n'existe pas d'élément prouvant que la disparition d'une concentration détectable d'anticorps expose un individu immunocompétent à un risque de contracter cette maladie.

Au Sri Lanka, une enquête transversale en communauté a été réalisée dans 3 districts (Colombo, Badulla et Killinochi) en 2014. L'ensemble des 4 tranches d'âge testées (9-11 mois, 3-4 ans, 7-9 ans et 15 ans) ont présenté des taux élevés de séroprévalence. Dans le groupe des enfants de 15 ans, les taux de séropositivité étaient respectivement de 97%, 100% et 75% contre les types 1,2 et 3.[40] Dans le cadre de cette étude et d'autres, la séroprévalence du type 3 diminuait avec l'âge, car les titres d'anticorps contre le type 3 sont plus faibles et chutent au-dessous du seuil de détectabilité plus tôt que les titres d'anticorps contre les types 1 et 2.

En Gambie, suite à la vaccination systématique, on a observé une légère baisse des concentrations d'anticorps contre le type 1 chez les enfants de 8-9 ans par rapport aux enfants de 3-4 ans, mais, dans les 2 tranches d'âge, les pourcentages d'enfants avec des anticorps détectables étaient pratiquement identiques (88 et 89%, respectivement). Les enfants de la tranche 8-9 ans étaient moins nombreux que ceux de la tranche 3-4 ans à posséder des anticorps contre le type 3 (78% contre 89%, p <0,001). Parmi les 67 enfants ayant reçu 2 doses de VPOt, >80% présentaient encore des anticorps neutralisants lorsqu'ils subissaient un dosage au bout de 5 ans.[41, 42] Le VPOb ayant été utilisé pour la première fois en 2009, la période écoulée depuis est relativement courte et on ne dispose pas de données à long terme sur la persistance des anticorps induits par ce vaccin. La plus forte immunogénicité initiale du VPOb par rapport au VPOt contre les types 1 et 3 laisse à penser que les anticorps formés suite à la vaccination par le VPOb devraient persister au moins autant, sinon plus, que ceux dont la production est induite par le VPOt.

Coadministration avec d'autres vaccins

Le VPO est actuellement administré en même temps que d'autres vaccins dont le bacille Calmette-Guérin (BCG), le vaccin antidiphtérique, antitétanique, anticoquelucheux (DTC), les vaccins contre l'hépatite B, la rougeole et *Haemophilus influenzae* type b (Hib), le vaccin antipneumococcique conjugué et/ou les vaccins antirotavirus. Aucune interférence en termes

[40] Gamage D et al. Achieving high seroprevalence against polioviruses in Sri Lanka-Results from a serological survey, 2014. J Epidemiol Glob Health. 2015 Dec;5(4 Suppl 1):S67–71

[41] Nishio O et al. The trend of acquired immunity with live poliovirus vaccine and the effect of revaccination: follow up of vaccinees for ten years. J Biol Standardization. 1984; 12(1):1–10.

[42] Cotation des preuves scientifiques – tableau III. Antibody persistence. Disponible uniquement en langue anglaise sur http://www.who.int/entity/immunization/polio_grad_duration_protection.pdf, consulté en février 2016.

of adverse events have been observed when tOPV was administered with these vaccines.[2, 43] Interference with the immune response to rotavirus vaccine when co-administered with OPV has been noted after the first dose but not after completion of the full primary series, while the response to the poliovirus types was unaffected.[44] No immunological interference with tOPV has been observed when given together with supplementary vitamin A.[2] The limited available evidence supports the safety and immunogenicity of co-administration of OPV and oral cholera vaccines.[45] Although no data are available for bOPV, it is assumed that, as for tOPV, no interference would occur between bOPV and the other routinely administered vaccines.

Immunocompromised persons as special risk groups

In a small proportion of individuals with a primary immunodeficiency disease, OPV immunization can lead to persistent iVDPV infections, with chronic shedding of iVDPVs that show regained neurovirulence, as demonstrated by genetic sequencing.[46] To date, approximately 100 persons with primary immunodeficiency diseases worldwide have been reported to be excreting iVDPVs.[17, 47] However, the true incidence of chronic iVDPV infections remains uncertain,[48] because only some infections lead to AFP, the primary marker for detection of poliomyelitis. To date, no iVDPV is known to have generated secondary cases with paralysis.

Data suggest that acquired (secondary) immunodeficiency syndromes, such as that caused by HIV infection, do not lead to prolonged poliovirus excretion after OPV vaccination.[49] HIV infection does not appear to be a risk factor for VAPP or paralytic poliomyelitis caused by WPV.[50] Although in many developing countries the immune status of infants is not known, the first doses of OPV are administered at an age when HIV infection would not have caused immunodeficiency. The immune response to OPV in HIV-infected and non-infected infants at standard routine immunization age does not appear to differ.[51]

d'efficacité ou d'augmentation de l'incidence des manifestations secondaires n'a été observée lors de l'administration du VPOt avec ces vaccins.[2, 43] Une interférence avec la réponse immunitaire au vaccin antirotavirus coadministré avec le VPO a été notée après la première dose, mais pas à l'achèvement de la série primaire, tandis que la réponse aux différents types de poliovirus n'était pas affectée.[44] Aucune interférence immunologique n'a été observée avec le VPOt lorsque ce vaccin était administré en même temps qu'une supplémentation en vitamine A.[2] Les éléments limités disponibles sont en faveur de l'innocuité et de l'immunogénicité de la coadministration du VPO et des vaccins anticholériques oraux.[45] Bien que l'on ne dispose d'aucune donnée pour le VPOb, on suppose que, comme pour le VPOt, aucune interférence ne devrait intervenir entre le VPOb et les autres vaccins administrés de manière systématique.

Personnes immunodéprimées en tant que groupe à risque particulier

Chez un faible pourcentage des individus souffrant d'un déficit immunitaire primaire, la vaccination avec le VPO peut entraîner des infections par des PVDVi persistantes, s'accompagnant de l'excrétion chronique de PVDVi ayant retrouvé une neurovirulence, comme le montre le séquençage génétique.[46] À ce jour, approximativement 100 personnes dans le monde présentant un immunodéficit primaire ont été signalées comme excrétant des PVDVi.[17, 47] Cependant, l'incidence vraie des infections chroniques par des PVDVi reste incertaine,[48] car seules certaines infections débouchent sur une PFA, le principal marqueur de la poliomyélite. À ce jour, on ne connaît pas de situation où un PVDVi aurait généré des cas secondaires avec paralysie.

Les données laissent à penser que les syndromes d'immunodéficience acquise (secondaire), tels que ceux provoqués par l'infection à VIH, n'entraînent pas l'excrétion prolongée de poliovirus après une vaccination avec le VPO.[49] L'infection par le VIH ne parait pas être un facteur de risque pour l'apparition d'une PPAV ou d'une poliomyélite paralytique due à un PVS.[50] Si, dans de nombreux pays en développement, le statut immunitaire des nourrissons n'est pas connu, les premières doses de VPO sont administrées à un âge où l'infection à VIH ne devrait pas avoir provoqué de déficit immunologique. La réponse immunitaire à l'administration du VPO à l'âge prévu par le calendrier de vaccination systématique ne semble pas différer entre les nourrissons infectés et non infectés par le VIH.[51]

[43] WHO prequalified vaccines [online database]; available at http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html, accessed February 2016.

[44] Patel M et al. Influence of oral polio vaccines on performance of the monovalent and pentavalent rotavirus vaccines. Vaccine. 2012; 30, Suppl 1, A30–A35.

[45] Kollaritsch H et al. Safety and Immunogenicity of Live Oral Cholera and Typhoid Vaccines Administered Alone or in Combination with Antimalarial Drugs, Oral Polio Vaccine, or Yellow Fever Vaccine. The Journal of Infectious Diseases 1997;175:871–875.

[46] Yang C et al. Intratypic recombination among lineages of type 1 vaccine-derived poliovirus emerging during chronic Infection of an immunodeficient patient, J Virol. 2005; 79(20): 12623–12634.

[47] See No.25, 2015, 309–320.

[48] Duintjer Tebbens RJ et al. Risks of paralytic disease due to wild or vaccine-derived poliovirus after eradication. Risk Analysis. 2006; 26(6):1471–1505.

[49] Hennessey KA et al. Poliovirus vaccine shedding among persons with HIV in Abidjan, Côte d'Ivoire. J Inf Dis. 2005; 192:2124–2128.

[50] Vernon A et al. Paralytic poliomyelitis and HIV infection in Kinshasa, Zaire. In: Proceedings of the Sixth International Conference on AIDS . San Francisco, CA; June 20–24,1990.

[51] Clements CJ et al. How about HIV infection and routine childhood immunization: a review. Bull World Health Organ. 1987; 65(6):905–911.

[43] WHO prequalified vaccines [online database]; Disponible sur http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html, consulté en février 2016.

[44] Patel M et al. Influence of oral polio vaccines on performance of the monovalent and pentavalent rotavirus vaccines. Vaccine. 2012; 30, Suppl 1, A30–A35.

[45] Kollaritsch H et al. Safety and Immunogenicity of Live Oral Cholera and Typhoid Vaccines Administered Alone or in Combination with Antimalarial Drugs, Oral Polio Vaccine, or Yellow Fever Vaccine. The Journal of Infectious Diseases 1997;175:871–875.

[46] Yang C et al. Intratypic recombination among lineages of type 1 vaccine-derived poliovirus emerging during chronic Infection of an immunodeficient patient, J Virol. 2005; 79(20): 12623–12634.

[47] Voir N° 25, 2015, 309-320.

[48] Duintjer Tebbens RJ et al. Risks of paralytic disease due to wild or vaccine-derived poliovirus after eradication. Risk Analysis. 2006; 26(6):1471–1505.

[49] Hennessey KA et al. Poliovirus vaccine shedding among persons with HIV in Abidjan, Côte d'Ivoire. J Inf Dis. 2005; 192:2124–2128.

[50] Vernon A et al. Paralytic poliomyelitis and HIV infection in Kinshasa, Zaire. In: Proceedings of the Sixth International Conference on AIDS . San Francisco, CA; June 20–24 1990.

[51] Clements CJ et al. How about HIV infection and routine childhood immunization: a review. Bull World Health Organ. 1987; 65(6):905–911.

Poliovirus antivirals are currently being developed for treatment of immunodeficient individuals in order to clear the infection in those who chronically shed poliovirus. The most advanced antiviral agent, pocapavir (V-073), a capsid inhibitor, has been shown to shorten poliovirus excretion following a challenge with OPV.[52] The development of additional antiviral candidates with differing mechanisms of action continues to be a priority (to prevent the emergence of resistance), with the goal of having at least 2 antiviral agents available for use in combination therapy for iVDPV excretors.

2. Inactivated poliovirus vaccine (IPV)

Vaccine characteristics

IPV is made from selected WPV strains – Mahoney or Brunhilde (type 1), MEF-1 (type2), and Saukett (type 3) – or from Sabin strains, and are now grown in Vero cell culture or in human diploid cells. An IPV based on the attenuated Sabin virus strains (sIPV) was developed and licensed in Japan in 2012. The advantages of sIPV are that biocontainment requirements are less stringent than for wild viruses and the consequences of any release of Sabin strains into populations would be less serious than with release of wild strains.[53]

All current IPV vaccines have substantially greater antigenicity than those produced in the 1950s, and are sometimes termed 'enhanced potency IPV' (eIPV). IPV manufacturing relies on inactivation of cell culture-derived polioviruses with formaldehyde, in a final formulation containing sufficient antigen units for each serotype.[54] IPV may contain formaldehyde, as well as traces of streptomycin, neomycin or polymyxin B. Some formulations of IPV contain 2-phenoxyethanol (0.5%) as a preservative for multi-dose vials. IPV formulations do not contain thiomersal, which is incompatible with IPV antigenicity. The vaccine should be refrigerated to preserve potency but not frozen as this could diminish potency. Current 10-dose and 5-dose IPV vials can be used according to the WHO multi-dose vial policy and kept for up to 28 days after opening.[55]

IPV is available either as a stand-alone product or in combination with one or more other vaccine antigens including DTP, hepatitis B, or Hib.

[52] McKinlay MA et al. Progress in the development of poliovirus antiviral agents and their essential role in reducing risks that threaten eradication. J Infect Dis. (2014) 210 (suppl 1): S447–S453.

[53] Bakker WAM et al. Inactivated polio vaccine development for technology transfer using attenuated Sabin poliovirus strains to shift from Salk-IPV to Sabin-IPV. Vaccine. 2011;29(41):7188–7196.

[54] Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (inactivated). WHO Technical Report Series 993, 2014. Geneva, World Health Organization. Available at http://who.int/biologicals/vaccines/Annex3_IPV_Recommendations_eng.pdf?ua=1, accessed February 2016.

[55] Application of WHO Multi-Dose Vial Policy for Inactivated Polio Vaccine. Available at http://www.who.int/immunization/diseases/poliomyelitis/inactivated_polio_vaccine/MDVP_Nov2014.pdf, accessed February 2016.

Des antiviraux visant les poliovirus sont actuellement en cours de mise au point pour le traitement des individus immunodéficients en vue d'éliminer l'infection chez ceux qui excrètent chroniquement de tels virus. Il a été démontré que l'agent antiviral dont le développement est le plus avancé, le pocapavir (V-073), un inhibiteur de liaison à la capside, abrégeait l'excrétion de poliovirus après une épreuve de provocation avec le VPO.[52] La mise au point d'autres antiviraux candidats avec des mécanismes d'action différents continue d'être une priorité (en vue de prévenir l'émergence d'une résistance), en se donnant comme objectif de disposer de 2 agents antiviraux au moins pour les utiliser sous forme de traitement combiné chez les excréteurs de PVDVi.

2. Vaccin antipoliomyélitique inactivé (VPI)

Caractéristiques du vaccin

Le VPI est préparé à partir de souches de PVS sélectionnées – Mahoney ou Brunhilde (type 1), MEF-1 (type 2) et Saukett (type 3) – ou à partir de souches Sabin, toutes ces souches étant maintenant cultivées sur des cellules Vero ou sur des cellules diploïdes humaines. Un VPI préparé à partir d'une souche virale Sabin atténuée (PVIs) a récemment été mis au point et homologué au Japon en 2012. Le PVIs a notamment comme avantages, par rapport aux poliovirus sauvages, des exigences moins strictes en matière de confinement biologique et une moindre gravité des conséquences d'une éventuelle diffusion des souches vaccinales parmi des populations.[53]

Tous les vaccins VPI actuels présentent une antigénicité substantiellement plus forte que ceux produits dans les années 1950 et sont parfois appelés VPI à activité améliorée. La fabrication du VPI repose sur l'inactivation au formaldéhyde de poliovirus dérivés sur culture cellulaire pour obtenir une formulation finale contenant suffisamment d'unités antigéniques pour chaque sérotype.[54] Le VPI peut contenir du formaldéhyde, ainsi que des traces de streptomycine, de néomycine ou de polymyxine B. Certaines formulations de VPI renferment du 2-phénoxyéthanol (0,5%) en tant que conservateur pour les flacons multidoses. Ces formulations ne font pas appel au thiomersal, qui est incompatible avec l'antigénicité du VPI. Les vaccins devront être réfrigérés pour préserver leur activité, mais la congélation est à éviter car elle pourrait diminuer cette même activité. Les flacons de 10 ou 5 doses de VPI actuellement disponibles peuvent être utilisés conformément à la politique de l'OMS relative aux flacons multidoses et conservés jusqu'à 28 jours après ouverture.[55]

Le VPI est disponible sous forme indépendante ou en association avec un ou plusieurs autres antigènes vaccinaux, dont ceux du DTP, du vaccin contre l'hépatite B ou du vaccin contre le Hib.

[52] McKinlay MA et al. Progress in the development of poliovirus antiviral agents and their essential role in reducing risks that threaten eradication. J Infect Dis. (2014) 210 (suppl 1): S447-S453.

[53] Bakker WAM et al. Inactivated polio vaccine development for technology transfer using attenuated Sabin poliovirus strains to shift from Salk-IPV to Sabin-IPV. Vaccine. 2011;29(41):7188–7196.

[54] Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (inactivated). WHO Technical Report Series 993, 2014. Genève, Organisation mondiale de la Santé. Disponible uniquement en langue anglaise à l'adresse suivante: http://who.int/biologicals/vaccines/Annex3_IPV_Recommendations_eng.pdf?ua=1, consulté en février 2016.

[55] Application of WHO Multi-Dose Vial Policy for Inactivated Polio Vaccine. Disponible sur http://www.who.int/immunization/diseases/poliomyelitis/inactivated_polio_vaccine/MDVP_Nov2014.pdf, consulté en février 2016.

According to manufacturer specifications, IPV can be administered by subcutaneous or intramuscular injection. When combined with an adjuvanted vaccine the injection must be intramuscular. A fractional dose of stand-alone IPV can also be administered via the intradermal route (see below).

Safety of IPV

IPV is considered very safe, whether given alone or in combination with other vaccines. There is no proven causal relationship with any adverse events other than transient minor local erythema (0.5%–1%), induration (3%–11%) and tenderness (14%–29%).[56, 57]

Immunogenicity, efficacy and effectiveness

IPV has been shown to be highly effective in eliciting humoral antibody responses to poliovirus in both high-income and low-income settings.[58, 59] In Sweden, IPV was used to eliminate poliovirus.[60, 61] In the USA a 2-dose schedule at 2 and 4 months of age achieved seroconversion in 95% of vaccine recipients for all 3 serotypes.[62] In Cuba, where WPVs stopped circulating decades ago and OPV is delivered only in 2 supplemental campaigns each year, 2 doses of IPV given at 4 and 8 months induced antibodies to type 1, 2 and 3 polioviruses in 100%, 100%, and 99.4% of vaccinees, respectively, and a 3-dose schedule given at 6, 10, and 14 weeks induced antibodies to type 1, 2, and 3 polioviruses in 94%, 83% and 100% of vaccine recipients, respectively.[63, 11, 64]

The immunogenicity of IPV schedules depends on the age at administration and number of doses, due to interference by maternal antibodies. A study of immunogenicity of a 3-dose schedule in Puerto Rico found seroconversion rates of 85.8%, 86.2% and 96.9% for serotypes 1, 2 and 3 respectively on a 6, 10, 14 week schedule, compared with 99.6%, 100% and 99.1% on a 2, 4, 6 month schedule.[65]

Conformément aux spécifications du fabricant, le VPI peut être administré par injection sous cutanée ou intramusculaire. Lorsqu'il est associé à un vaccin adjuvanté, l'injection doit être intramusculaire. Une dose fractionnée de VPI en formulation indépendante peut aussi être administrée par voie intradermique (vois plus loin).

Innocuité du VPI

Le VPI est considéré comme très sûr, qu'il soit administré seul ou en combinaison avec d'autres vaccins. Il n'existe pas de relation de causalité prouvée avec une manifestation indésirable autre qu'un érythème local transitoire mineur (0,5-1%), une induration (3-11%) ou une douleur à la palpation (14-29%).[56, 57]

Immunogénicité, efficacité et efficience

Le VPI s'est révélé hautement efficace dans la génération de réponses en anticorps humorales aux poliovirus dans les pays à revenu élevé, comme dans ceux disposant de revenus plus faibles.[58, 59] En Suède, le VPI a été utilisé pour éliminer les poliovirus.[60, 61] Aux États-Unis, un calendrier comprenant 2 doses administrées à 2 et 4 mois a permis d'obtenir un taux de séroconversion de 95% chez les bénéficiaires de la vaccination pour l'ensemble des 3 sérotypes.[62] À Cuba, où les PVS ont cessé de circuler il y a plusieurs décennies et où le VPO n'est délivré que dans le cadre de 2 campagnes supplémentaires par an, 2 doses de VPI administrées à 4 et 8 mois induisaient la formation d'anticorps contre les poliovirus de types 1, 2 et 3 chez respectivement 100, 100 et 99,4% des personnes vaccinées et un calendrier en 3 doses, administrées à 6, 10 et 14 semaines générait une réponse en anticorps contre les poliovirus de types 1, 2 et 3, respectivement chez 94%, 83% et 100% des personnes vaccinées.[63, 11, 64]

L'immunogénicité des calendriers vaccinaux incluant le VPI dépend de l'âge d'administration et du nombre de doses en raison de l'interférence avec les anticorps maternels. Une étude examinant l'immunogénicité d'un calendrier en 3 doses à Porto Rico a relevé des taux de séroconversion de 85,8%, 86,2% et 96,9% pour les sérotypes 1, 2 et 3 respectivement avec un calendrier de vaccination à 6, 10 et 14 semaines, contre des taux de 99,6%, 100% et 99,1% avec un calendrier de vaccination à 2, 4 et 6 mois.[65]

[56] Vidor E et al. Poliovirus vaccine-inactivated. In Plotkin SA, Orenstein WA, Offit PA. Vaccines, 2013, 6th edition 2013. Philadelphia: Elsevier-Saunders, pp. 573–597.

[57] Iqbal S et al. Preparation for global introduction of inactivated poliovirus vaccine: safety evidence from the US Vaccine Adverse Event Reporting System, 2000–12. Lancet Infect Dis 2015. Volume 15, No. 10, p1175–1182, October 2015.

[58] Vidor E et al. The place of DTP/eIPV vaccine in routine paediatric vaccination. Rev Med Virol. 1994; 4:261–277.

[59] Grading of scientific evidence – table IV: Efficacy/effectiveness of IPV. Available at http://www.who.int/immunization/polio_grad_ipv_effectiveness.pdf, accessed February 2016.

[60] Böttiger M Polio immunity to killed vaccine: an 18-year follow-up. Vaccine. 1990 Oct;8(5):443–445.

[61] Böttiger M. The elimination of polio in the Scandinavian countries. Public Health Rev. 1993-1994;21(1-2):27–33.

[62] Faden H et al. Comparative evaluation of immunization with live attenuated and enhanced-potency inactivated trivalent poliovirus vaccines in childhood: systemic and local immune responses. J Inf Dis. 1990; 162:1291–1297.

[63] Cuba IPV Study collaborative group. Randomized, placebo- controlled trial of inactivated polio virus in Cuba. New Eng Med J. 2007; 356:1536–1544.

[64] Resik S et al. Priming after a fractional dose of inactivated poliovirus vaccine. New Eng J Med. 2013; 368:416–424.

[65] Dayan GH et al. Serologic response to inactivated polio vaccine: a randomized clinical trial comparing 2 vaccination schedules in Puerto Rico. J Inf Dis. 2007; 195:12–20.

[56] Vidor E et al. Poliovirus vaccine-inactivated. In O. W. Plotkin SA, Orenstein WA, Offit PA. Vaccines, 2013, 6th edition 2013. Philadelphia: Elsevier-Saunders, pp. 573–597.

[57] Iqbal S et al. Preparation for global introduction of inactivated poliovirus vaccine: safety evidence from the US Vaccine Adverse Event Reporting System, 2000–12. Lancet Infect Dis 2015. Volume 15, No. 10, p1175–1182, October 2015.

[58] Vidor E et al. The place of DTP/eIPV vaccine in routine paediatric vaccination. Rev Med Virol. 1994; 4:261–277.

[59] Cotation des preuves scientifiques – tableau IV. Efficacy/effectiveness of IPV. Disponible uniquement en langue anglaise sur http://www.who.int/immunization/polio_grad_ipv_effectiveness.pdf, consulté en février 2016.

[60] Böttiger M Polio immunity to killed vaccine: an 18-year follow-up. Vaccine. 1990 Oct;8(5):443–445.

[61] Böttiger M.The elimination of polio in the Scandinavian countries. Public Health Rev. 1993-1994;21(12):27–33.

[62] Faden H et al. Comparative evaluation of immunization with live attenuated and enhanced-potency inactivated trivalent poliovirus vaccines in childhood: systemic and local immune responses. J Inf Dis. 1990; 162:1291–1297.

[63] Cuba IPV Study collaborative group. Randomized, placebo- controlled trial of inactivated polio virus in Cuba. New Eng Med J. 2007; 356:1536–1544.

[64] Resik S et al. Priming after a fractional dose of inactivated poliovirus vaccine. New Eng J Med. 2013; 368:416–424.

[65] Dayan GH et al. Serologic response to inactivated polio vaccine: a randomized clinical trial comparing 2 vaccination schedules in Puerto Rico. J Inf Dis. 2007; 195:12–20.

IPV is less effective than OPV in inducing intestinal mucosal immunity in previously unvaccinated individuals. Children given IPV then challenged with OPV become infected and shed OPV in their faeces. Nonetheless, IPV can reduce the quantity and duration of virus shedding in faeces, which may contribute to a reduction in transmission. It has been suggested that IPV may have a greater impact on oropharyngeal shedding, although there is limited evidence to support this observation.[66] However, two studies have shown that IPV is more effective than an additional dose of OPV in reducing shedding in previously OPV-vaccinated children.[67, 68]

Differences in reduction of shedding by OPV and IPV may be illustrated by the persistent circulation of WPV in Israel in 2013,[69] suggesting that WPV transmission can be sustained for months if undetected in areas with high IPV coverage where local factors facilitate transmission (e.g. poor hygiene and living conditions).[70]

A systematic review of seroconversion rates after a single dose of IPV given at or shortly after birth (<7 days after birth) found a seroconversion rate of 8%–100% for type 1, 15%–100% for type 2, and 15%–94% for type 3, measured at 4–6 weeks of age.[35] The wide range of seroconversion rates is probably due to differing levels of interference by maternal antibodies. Seroconversion was strongly dependent on the age at vaccination. Even in the absence of seroconversion, IPV may prime individuals for a subsequent booster dose. In a large randomized controlled trial in Cuba, among infants aged 4 months, 63% seroconverted to type 2 following a single full dose of IPV administered intramuscularly, and 98% of infants who did not seroconvert were successfully primed (i.e. developed detectable antibody within 7 days of receiving a second dose, which would not be expected in a naïve population).[64, 71, 72] Thus, either seroconversion or priming resulted from a full dose of IPV in 99% of study infants; the extent to which priming alone would provide protection from paralysis upon reinfection remains unknown. In Hungary VAPP disappeared following the introduction of a sequential schedule using 1 dose of IPV before OPV. However, investigation of a WPV1 poliomyelitis outbreak

Le VPI offre une moindre efficacité que le VPO dans l'induction d'une immunité mucosale intestinale chez les individus auparavant non vaccinés. Des enfants ayant reçu le VPI et subissant par la suite une épreuve de provocation par le VPO ont été infectés et ont excrété le VPO dans leurs selles. Néanmoins, le VPI est susceptible de diminuer l'ampleur et la durée de l'excrétion virale dans les selles, ce qui peut contribuer à réduire la transmission. Il a été suggéré que le VPI pouvait avoir un impact plus important sur l'excrétion oropharyngée, même si les preuves à l'appui de cette observation sont limitées.[66] Toutefois, deux études ont montré que le VPI était plus efficace qu'une dose supplémentaire de VPO pour réduire l'excrétion chez des enfants antérieurement vaccinés avec le VPO.[67, 68]

Les différences entre les réductions de l'excrétion obtenues avec le VPO et le VPI ont été illustrées notamment par la circulation persistante de PVS en Israël en 2013,[69] ce qui amène à penser que la transmission de tels virus peut rester soutenue pendant plusieurs mois si elle n'est pas détectée dans des zones de forte couverture par le VPI, où des facteurs locaux facilitent la transmission (conditions d'hygiène et de de vie médiocres, par exemple).[70]

Une étude systématique des taux de séroconversion après l'administration d'une dose unique de VPI à la naissance ou peu de temps après (<7 jours après celle-ci) a relevé un taux de séroconversion de 8-100% contre le type 1, de 15-100% contre le type 2, et de 15-94% contre le type 3, lors d'un dosage à 4-6 semaines.[35] La plage de variation étendue des taux de séroconversion est probablement imputable à la diversité des niveaux d'interférence des anticorps maternels. La séroconversion était fortement dépendante de l'âge lors de la vaccination. Même en l'absence de séroconversion, le VPI pourrait réaliser un amorçage de la réponse immunitaire des individus en attendant une dose de rappel ultérieure. Dans le cadre d'un essai contrôlé et randomisé de grande ampleur, mené chez des enfants cubains de 4 mois, 63% des sujets ont subi une séroconversion contre le type 2 après l'administration d'une dose unique complète de VPI par voie intramusculaire, et 98% des nourrissons non séroconvertis ont bénéficié d'un amorçage réussi de la réponse immunitaire (c'est-à-dire qu'ils ont produit une réponse en anticorps détectable dans les 7 jours suivant la réception d'une seconde dose, pourcentage qu'on ne s'attend pas à observer dans une population naïve).[64, 71, 72] Ainsi, l'administration d'une dose complète de VPI a entraîné une séroconversion ou un amorçage de la réponse immunitaire chez 99% des nourrissons étudiés, l'ampleur de la protection conférée par

[66] Marine WM et al. Limitation of fecal and pharyngeal poliovirus excretion in Salk-vaccinated children. A family study during a type 1 poliomyelitis epidemic. Am J Hyg. 1962; 76:173–195.

[67] Jafari H et al. Efficacy of inactivated poliovirus vaccine in India. Science 2014;345:922–925.

[68] John J et al. Effect of a single inactivated poliovirus vaccine dose on intestinal immunity against poliovirus. Lancet. 2014; Oct 25 384(9953):1505–1512.

[69] Anis E. Insidious reintroduction of wild poliovirus into Israel, 2013. Euro Surv. 2013; Sep 19; 18(38).

[70] Kalkowska DA et al. Modeling options to manage type 1 wild poliovirus imported into Israel in 2013. J Infect Dis 2015;211(11):1800–1812.

[71] Priming is defined as the absence of seroconversion after the first IPV dose along with an antibody titre at 8 months, 7 days, 4 times greater than the titre at 8 months; or an undetectable reciprocal titre at 8 months and a detectable reciprocal titre at 8 months, 7 days.

[72] Robertson SE et al. Clinical efficacy of a new, enhanced-potency, inactivated poliovirus vaccine. Lancet. 1988; Apr 23; 1(8591):897–899.

[66] Marine WM et al. Limitation of fecal and pharyngeal poliovirus excretion in Salk-vaccinated children. A family study during a type 1 poliomyelitis epidemic. Am J Hyg. 1962; 76:173–195.

[67] Jafari H et al. Efficacy of inactivated poliovirus vaccine in India. Science 2014;345:922–925.

[68] John J et al. Effect of a single inactivated poliovirus vaccine dose on intestinal immunity against poliovirus. Lancet. 2014; Oct 25 384(9953):1505–1512.

[69] Anis E. Insidious reintroduction of wild poliovirus into Israel, 2013. Euro Surv. 2013; Sep 19; 18(38).

[70] Kalkowska DA et al. Modeling options to manage type 1 wild poliovirus imported into Israel in 2013. J Infect Dis 2015;211(11):1800–1812.

[71] Priming is defined as the absence of seroconversion after the first IPV dose along with an antibody titre at 8 months, 7 days, 4 times greater than the titre at 8 months; or an undetectable reciprocal titre at 8 months and a detectable reciprocal titre at 8 months, 7 days.

[72] Robertson SE et al. Clinical efficacy of a new, enhanced-potency, inactivated poliovirus vaccine. Lancet. 1988; Apr 23; 1(8591):897–899.

showed effectiveness for 1 and 2 IPV doses of 36% and 89%, respectively, consistent with seroconversion rates for the serotype after 1 and 2 doses. Other trials have demonstrated that earlier administration of 1 dose of IPV (e.g. at 6–8 weeks) gave much lower type 2 seroconversion rates of 32%–39%.[23, 73]

Intradermal IPV administration with fractional doses of IPV (0.1mL or 1/5 of a full dose) offers potential cost reduction and allows immunization of a larger number of persons with a given vaccine supply.[74] Studies have generally demonstrated that a single fractional dose of IPV (1/5 of the full dose) gives lower seroconversion rates than a full dose but after 2 doses the rates are similar to those after 2 full doses. In all cases the median antibody titres induced by the 2 fractional doses, although high, were lower than with the 2 full doses. In studies in Cuba[64] and in Bangladesh,[74] 2 doses of fractional-dose IPV induced seroconversion rates of 98% to type 2 poliovirus in Cuba (when given at age 4 and 8 months) and 81% to type 2 poliovirus in Bangladesh (when given at 6 and 14 weeks). The results indicate that 2 fractional doses of IPV provide higher seroconversion rates than a single full dose, as shown in Cuba (63% when given at age 4 months) and in Bangladesh (39% when given at age 6 weeks). This approach, using 2 fractional doses instead of 1 full dose, increases the immunogenicity of IPV and can extend coverage if supplies are limited.

Duration of protection

Information on the duration of IPV-induced protection from high-income countries indicates that circulating antibody persists for decades and possibly for life. However, as antibody titres decrease over time, some adults may lack detectable antibody. Persisting neutralizing antibodies against polioviruses are usually found in all vaccine recipients 5 years after the primary immunization series of 3–4 doses.[75, 76] Neutralizing antibodies were found in all of 250 young adults (18 years) in

cet amorçage seul contre la paralysie en cas de réinfection restant cependant inconnue. En Hongrie, la PPAV a disparu suite à l'introduction d'un calendrier séquentiel prévoyant 1 dose de VPI avant l'administration du VPO. Néanmoins, l'investigation d'une flambée de poliomyélite due à un PVS a mis en évidence une efficacité pour 1 dose et 2 doses de VPI de 36 et 89% respectivement, cohérente avec les taux de séroconversion pour le sérotype considéré après 1 et 2 doses. D'autres essais ont montré que l'administration plus précoce d'une dose de VPI (par exemple à 6-8 semaines) donnait des taux de séroconversion contre le type 2 bien plus bas de 32 à 39%.[23, 73]

L'administration intradermique de doses fractionnées de VPI (0,1 ml ou 1/5 de la dose complète) offre la possibilité de réduire les coûts et de vacciner un plus grand nombre de personnes avec un stock de vaccin donné.[74] Des études montrent qu'en général une seule dose fractionnée de VPI (1/5 de la dose complète) donne des taux de séroconversion plus faibles qu'une dose complète, mais qu'après l'administration de 2 doses fractionnées, les taux sont similaires à ceux obtenus après 2 doses complètes. Dans tous les cas, les valeurs médianes des titres d'anticorps induits par les doses fractionnées, bien qu'élevées, sont plus faibles que pour les doses complètes. Dans le cadre d'études menées à Cuba[64] et au Bangladesh,[74] 2 doses fractionnées de VPI ont induit des taux de séroconversion de 98% contre les poliovirus de type 2 à Cuba (lorsqu'elles étaient administrées à l'âge de 4 et 8 mois) et de 81% contre les poliovirus de type 2 au Bangladesh (lorsqu'elles étaient administrées à l'âge de 6 et 14 semaines). Ces résultats indiquent que 2 doses fractionnées de VPI conduisent à des taux de séroconversion plus élevés qu'une dose unique complète, comme cela a été montré à Cuba (63% avec une administration à 4 mois) et au Bangladesh (39% avec une administration à 6 semaines). Cette approche consistant à utiliser 2 doses fractionnées au lieu d'une dose unique accroît l'immunogénicité du PVI et peut permettre d'étendre davantage la couverture vaccinale lorsque les approvisionnements sont limités.

Durée de la protection

Les informations relatives à la durée de la protection induite par le VPI émanant de pays à revenu élevé indiquent que la présence d'anticorps circulants persiste sur des décennies (et potentiellement, sur le vie entière). Néanmoins, comme les titres d'anticorps diminuent avec le temps, ils ne sont parfois plus détectables chez certains adultes. On observe habituellement la persistance d'anticorps neutralisants contre les poliovirus chez toute les personnes vaccinées 5 ans après l'administration de la série vaccinale primaire de 3-4 doses.[75, 76] On a retrouvé des

[73] Simasathien S et al. Comparison of enhanced potency inactivated poliovirus vaccine (EIPV) versus standard oral poliovirus vaccine (OPV) in Thai infants. Scand J Inf Dis. 1994; 26:731–738.

[74] Anand A et al Early priming with inactivated poliovirus vaccine (IPV) and intradermal fractional dose IPV administered by a microneedle device: A randomized controlled trial. Vaccine, 2015 Nov 27;33(48):6816–6822.

[75] Carlsson RM et al. Antibody persistence in five-year-old children who received a pentavalent combination vaccine in infancy. Ped Inf Dis J. 2002; 21(6):535–541.

[76] Langue J et al. Persistence of antibodies at 5-6 years of age for children who had received a primary series vaccination with a pentavalent whole-cell pertussis vaccine and a first booster with a pentavalent acellular pertussis vaccine. Vaccine, 2004; 22(11-12):1406–1414.

[73] Simasathien S et al. Comparison of enhanced potency inactivated poliovirus vaccine (EIPV) versus standard oral poliovirus vaccine (OPV) in Thai infants. Scand J Inf Dis. 1994; 26:731–738.

[74] Anand A et al Early priming with inactivated poliovirus vaccine (IPV) and intradermal fractional dose IPV administered by a microneedle device: A randomized controlled trial. Vaccine, 2015 Nov 27;33(48):6816–6822.

[75] Carlsson RM et al. Antibody persistence in five-year-old children who received a pentavalent combination vaccine in infancy. Ped Inf Dis J. 2002; 21(6):535–541.

[76] Langue J et al. Persistence of antibodies at 5-6 years of age for children who had received a primary series vaccination with a pentavalent whole-cell pertussis vaccine and a first booster with a pentavalent acellular pertussis vaccine. Vaccine, 2004; 22(11-12):1406–1414.

Sweden who had received 3 doses of IPV as infants with a booster dose either at 6 or 10 years of age.[60, 77]

Although antibody may decline over time in some individuals, and may fall below detectable levels, there is no evidence that this leads to increased susceptibility to poliomyelitis (paralytic disease).[38] Almost all high-income countries use 3 or more doses of IPV. The long-term protection afforded by a single dose of IPV is under investigation.

Co-administration with other vaccines

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, rotavirus vaccines[39] /or measles-containing vaccines.[78]

Immunocompromised and special risk groups

In some countries that routinely use OPV, IPV is given instead of OPV to special risk groups, including HIV-infected infants. One study showed that 80% of HIV-infected children, with a presumed intact immune system, seroconverted after 2 doses of IPV.[79] Haemophiliac adults responded to IPV but HIV infection in this group had a negative effect on the overall titre levels.[80] Patients with chronic renal failure[81] and re-immunized patients after bone-marrow transplantation[82] responded well, although at least 2 doses of IPV were needed.

Co-administration of OPV and IPV

In developing country settings the concurrent administration of tOPV and IPV has induced uniformly high antibody responses to all 3 poliovirus types, consistent with responses induced by multiple doses of polio vaccines. A study conducted in 3 countries – Gambia, Oman and Thailand – comparing an OPV birth dose plus either OPV at 6, 10 and 14 weeks or OPV and IPV simultaneously at 6, 10 and 14 weeks, found that in Gambia and Oman, infants who received IPV and OPV simultaneously had the highest seroconversion rates. In Thailand, the seroconversion rates were similar in both groups.[29] In Pakistan comparison of the serological responses to various OPV or IPV schedules, or combined

anticorps neutralisants chez tous les membres d'un groupe de 250 jeunes adultes suédois (18 ans) ayant reçu 3 doses de VPI dans leur petite enfance, avec une dose de rappel à l'âge de 6 ou 10 ans. [60, 77]

Même si les titres d'anticorps diminuent avec le temps chez certains individus et peuvent passer au-dessous du seuil de détectabilité, il n'existe aucune preuve que ce phénomène conduise à une augmentation de la sensibilité à la poliomyélite (forme paralytique).[38] Presque tous les pays à revenu élevé utilisent 3 doses de VPI ou plus. La protection à long terme apportée par une dose unique de VPI est en cours d'étude.

Coadministration avec d'autres vaccins

Aucune interférence d'importance clinique n'a été rapportée lorsque le VPI était administré en association avec des vaccins homologués antidiphtériques-antitétaniques à composante coquelucheuse acellulaire ou à cellules entières, contre le Hib, l'hépatite B ou les rotavirus, avec le vaccin antipneumococcique polyosidique conjugué[39] ou encore avec des vaccins renfermant une composante rougeole.[78]

Individus immunodéprimés et groupes à risque particuliers

Certains pays utilisant systématiquement le VPO administrent le VPI au lieu du VPO à des groupes à risque particuliers, dont les nourrissons infectés par le VIH. Une étude a mis en évidence que 80% des enfants infectés par le VIH, avec un système immunitaire présumé intact, avaient manifesté une séroconversion après 2 doses de VPI.[79] Des adultes hémophiles ont répondu au VPI, mais, dans ce groupe, l'infection par le VIH a eu un effet négatif sur le niveau global des titres.[80] Des patients atteints d'une insuffisance rénale chronique[81] et d'autres revaccinés après une greffe de moelle osseuse[82] ont bien répondu, mais 2 doses au moins de VPI ont été nécessaires

Coadministration du VPO et du VPI

Dans des pays en développement, l'utilisation simultanée du VPO et du VPI a induit des réponses en anticorps uniformément fortes contre les 3 types de poliovirus, cohérentes avec l'emploi plusieurs de vaccins antipoliomyélitiques en doses multiples. Une étude menée dans 3 pays – la Gambie, l'État d'Oman et la Thaïlande – et comparant, après l'injection d'une dose de VPO à la naissance, l'administration d'une dose de VPO à 6, 10, et 14 semaines à l'administration simultanée du VPO et du VPI à 6, 10 et 14 semaines, a constaté qu'à Gambie, Oman et en, les nourrissons qui avaient reçu simultanément le VPO et le VPI présentaient les taux de séroconversion les plus élevés. En Thaïlande, les taux de séroconversion étaient similaires dans les 2 groupes.[29] Au Pakistan, la comparaison des réponses sérolo-

[77] Von Magnus H et al. Vaccination with inactivated poliovirus vaccine and oral poliovirus vaccine in Denmark. Rev Inf Dis. 1984; 6(Suppl.):S471–S474.

[78] Klein NP et al. An open-label, randomized, multi-center study of the immunogenicity and safety of DTaP-IPV (Kinrix™) co-administered with MMR vaccine with or without varicella vaccine in healthy pre-school age children. Vaccine. 2012 Jan 11;30(3):668–674.

[79] Barbi M et al. Antibody response to inactivated polio vaccine (E-IPV) in children born to HIV positive mothers. Euro J Epidem. 1992; 8:211–216.

[80] Varon D et al. Response of hemophilic patients to poliovirus vaccination: correlation with HIV serology and with immunological parameters. J Med Virol. 1993; 40:91–95.

[81] Sipila R et al. Good seroresponse to enhanced-potency inactivated poliovirus vaccine in patients on chronic dialysis. Nephrol Dialysis Transplant. 1990; 5:352–355.

[82] Engelhard D et al. Immune response to polio vaccination in bone marrow transplant recipients. Bone Marrow Transplant. 1991; 8:295–300.

[77] Von Magnus H et al. Vaccination with inactivated poliovirus vaccine and oral poliovirus vaccine in Denmark. Rev Inf Dis. 1984; 6(Suppl.):S471–S474.

[78] Klein NP et al. An open-label, randomized, multi-center study of the immunogenicity and safety of DTaP-IPV (Kinrix™) co-administered with MMR vaccine with or without varicella vaccine in healthy pre-school age children. Vaccine. 2012 Jan 11;30(3):668–674.

[79] Barbi M et al. Antibody response to inactivated polio vaccine (E-IPV) in children born to HIV positive mothers. Euro J Epidem. 1992; 8:211–216.

[80] Varon D et al. Response of hemophilic patients to poliovirus vaccination: correlation with HIV serology and with immunological parameters. J Med Virol. 1993; 40:91–95.

[81] Sipila R et al. Good seroresponse to enhanced-potency inactivated poliovirus vaccine in patients on chronic dialysis. Nephrol Dialysis Transplant. 1990; 5:352–355.

[82] Engelhard D et al. Immune response to polio vaccination in bone marrow transplant recipients. Bone Marrow Transplant. 1991; 8:295–300.

schedules, confirmed the favourable immunological response to combined IPV+OPV vaccination.[83] Combined IPV+OPV schedules appear to correct for the lower immunogenicity of OPV in developing countries.

The clinical impact of combined IPV+OPV vaccination was demonstrated in the Gaza Strip, where the incidence of paralytic poliomyelitis had remained high (≥10 cases/100 000 inhabitants) despite 90% coverage with OPV. Following the change from OPV alone to joint IPV+OPV vaccination in 1978, (i.e. tOPV at 1 month, followed by IPV+tOPV given at 2.5 months and 4 months, then tOPV at 5.5 months and 12 months), the annual incidence of paralytic poliomyelitis fell from 10 to 2.2/100 000 inhabitants during the first 3 years and during the following 5 years (1981–1985) to 0.16/100 000 inhabitants.[84]

Sequential use of IPV and OPV

Sequential administration of IPV followed by OPV appears to reduce or prevent VAPP while maintaining the high levels of intestinal mucosal immunity conferred by OPV. Sequential schedules of IPV followed by 2 or more doses of OPV have been used or studied in several countries including Israel, Oman, Pakistan, UK and USA. Such schedules reduce the number of doses of IPV and may theoretically optimize both the humoral and mucosal immunogenicity of polio vaccines. This approach effectively prevented poliomyelitis caused by VAPP in Denmark[64] using a schedule of 3 doses of IPV followed by 3 doses of OPV, in Hungary[11] using a schedule of 1 dose of IPV followed by 3 doses of OPV, and in the USA[85] which recommended 2 doses of IPV prior to 2 doses of OPV during the period of transition from use of an OPV-only schedule to an IPV-only schedule.

Previous studies also suggest that a single dose of IPV will effectively close immunity gaps to poliovirus type 2 (and types 1 and 3) in previously tOPV-vaccinated children.[86, 87] In addition, 2 recent studies in India found that in infants and children with a history of multiple doses of OPV, a single dose of IPV boosted intestinal mucosal immunity and reduced by 38%–76% the prevalence of excretion (depending on age group) after an

giques à divers calendriers de vaccination utilisant le VPO ou le VPI, ou encore à des calendriers combinés, a confirmé que le résultat le plus favorable était obtenu avec la vaccination combinée VPI +VPO.[83] L'administration de calendriers combinés VPI + VPO semble corriger la plus faible immunogénicité du VPO dans les pays en développement.

L'impact clinique de la vaccination combinée VPI + VPO a été démontré dans la Bande de Gaza, où l'incidence de la poliomyélite paralytique était restée forte (≥10 cas/100 000 habitants), malgré un taux de couverture de 90% par le VPO. Suite au passage du VPO seul à la vaccination simultanée par le VPI et le VPO en 1978 (c'est-à-dire l'administration du VPOt à 1 mois, suivie de celle de la combinaison VPI+VPOt à 2,5 mois et à 4 mois, puis dc celle du VPOt à 5,5 mois et à 12 mois), l'incidence annuelle de la poliomyélite paralytique a chuté de 10 à 2,2 cas pour 100 000 habitants pendant les 3 premières années, puis à 0,16 cas/100 000 habitants au cours des 5 années suivantes (1981-1985).[84]

Utilisation séquentielle du VPI et du VPO

L'administration séquentielle du VPI suivie de celle du VPO semble réduire ou prévenir la PPAV, tout en maintenant les niveaux élevés d'immunité mucosale intestinale conférés par le VPO. Des calendriers séquentiels prévoyant l'administration du VPI, puis celle de 2 doses ou plus de VPO ont été mis en œuvre ou étudiés dans plusieurs pays, dont Israël, Oman, le Pakistan, le Royaume-Uni et les États-Unis d'Amérique. Ces calendriers permettent de réduire le nombre de doses de VPI et théoriquement d'optimiser à la fois l'immunogénicité humorale et l'immunogénicité mucosale des vaccins antipoliomyélitiques. Cette approche a prévenu avec efficacité la poliomyélite sous forme de PPAV au Danemark,[64] où l'on a utilisé un calendrier comprenant 3 doses de VPI suivies de 3 doses de VPO, en Hongrie,[11] où le calendrier de vaccination prévoyait 1 dose de VPI suivie de 3 doses de VPO, et aux États-Unis d'Amérique,[85] où il était recommandé d'administrer 2 doses de VPI avant 2 doses de VPO pendant la période de transition entre l'utilisation d'un calendrier comprenant seulement des doses de VPO et celle d'un calendrier à base de VPI uniquement.

Des études antérieures amènent également à penser qu'une dose unique de VPI comblera efficacement les lacunes immunitaires à l'égard du poliovirus de type 2 (et de ceux des types 1 et 3) chez les enfants antérieurement vaccinés avec le VPOt.[86, 87] En outre, 2 études récemment menées en Inde ont constaté que chez des nourrissons et des enfants ayant reçu par le passé plusieurs doses de VPO, l'administration d'une dose unique de VPI renforçait l'immunité mucosale intestinale et réduisait

[83] du Chatelet IP et al. Serological response and poliovirus excretion following different combined oral and inactivated poliovirus vaccines immunization schedules. Vaccine. 2003; 21:1710–1718.

[84] Goldblum N et al. Poliomyelitis control in Israel, the West Bank and Gaza Strip: changing strategies with the goal of eradication in an endemic area. Bull World Health Organ.1994; 72(5):783–796.

[85] Alexander LN et al. Vaccine policy changes and epidemiology of poliomyelitis in the United States. JAMA. 2004; 292(14):1696–1701.

[86] Hanlon P et al. Serological comparisons of approaches to polio vaccination in the Gambia. Lancet.1987; 1(8536):800–801.

[87] Moriniere BJ et al. Immunogenicity of a supplemental dose of oral versus inactivated poliovirus vaccine. Lancet. 1993; Jun 19; 341(8860):1545–1550.

[83] du Chatelet IP et al. Serological response and poliovirus excretion following different combined oral and inactivated poliovirus vaccines immunization schedules. Vaccine. 2003; 21:1710–1718.

[84] Goldblum N et al. Poliomyelitis control in Israel, the West Bank and Gaza Strip: changing strategies with the goal of eradication in an endemic area. Bull World Health Organ.1994; 72(5):783–796.

[85] Alexander LN et al. Vaccine policy changes and epidemiology of poliomyelitis in the United States. JAMA. 2004; 292(14):1696–1701.

[86] Hanlon P et al. Serological comparisons of approaches to polio vaccination in the Gambia. Lancet.1987; 1(8536):800–801.

[87] Moriniere BJ et al. Immunogenicity of a supplemental dose of oral versus inactivated poliovirus vaccine. Lancet. 1993; Jun 19; 341(8860):1545–1550.

OPV challenge, compared to no polio vaccination.[88, 89] These studies also indicated that IPV is more effective in boosting intestinal mucosal immunity than OPV among OPV-immunized individuals.[67]

There are few data specifically showing benefits of a dose of OPV in IPV-vaccinated individuals. Limited results from a clinical trial in Gambia showed no significant differences in seroconversion in infants who had either an OPV or IPV primary series followed by an OPV booster at 1 year (OPV–OPV versus IPV–OPV).[86, 90]

A recent study in India assessed a schedule with bOPV followed by the simultaneous administration of bOPV+IPV; bOPV was administered at birth, 6 and 10 weeks, and bOPV+IPV at 14 weeks. This schedule, 4 doses of bOPV and 1 dose of IPV, resulted in excellent seroconversion rates (>99% to poliovirus type 1, 69%–78% to type 2, and >98% to type 3).[91]

A recent study in Chile assessed a sequential schedule, using IPV at 2 months followed by 2 doses of bOPV at 4 and 6 months. The resulting seroconversion rates were >98% to poliovirus type 1, >80% to type 2, and >98% to type 3, respectively, indicating high immunogenicity with this schedule.[92]

Cost-effectiveness of eradication

An economic analysis of polio eradication as a strategy reflected the status of the programme as of February 2010, including full consideration of post-eradication policies. For cost-effectiveness analysis of the eradication interventions, current pre-eradication experiences and two distinct potential future post-eradication vaccination policies were considered. Routine vaccination for polio without specific eradication activities was used as a comparator. Poliomyelitis incidence was estimated using a dynamic infection transmission model and costs based on numbers of vaccinated children. The polio eradication strategy using tOPV followed by OPV cessation after successful WPV eradication was found to be highly cost-effective based on standard criteria.

de 38 à 76% la prévalence de l'excrétion de poliovirus (selon la tranche d'âge) après une épreuve de provocation avec le VPO, par comparaison avec l'absence de vaccination contre la poliomyélite.[88, 89] Ces études ont également indiqué une plus grande efficacité du VPI par rapport au VPO dans le renforcement de l'immunité mucosale intestinale chez les individus vaccinés par le VPO.[67]

On dispose de peu de données attestant spécifiquement des bénéfices d'une dose de VPO chez les individus vaccinés avec le VPI. Les résultats limités d'un essai clinique réalisé en Gambie n'ont fait apparaître aucune différence significative dans la séroconversion des nourrissons ayant reçu soit une série primaire de doses de VPO, soit une série primaire de doses de VPI, suivie d'une dose de rappel de VPO à 1 an (VPO-VPO contre VPI-VPO).[86, 90]

Une étude récemment réalisée en Inde a évalué un calendrier prévoyant l'administration de VPOb suivie de l'injection simultanée des vaccins VPOb + VPI; le VPOb a été administré à la naissance et à 6 et 10 semaines, tandis que la combinaison VPOb + VPI était délivrée à 14 semaines. Ce calendrier comprenant 4 doses de VPOb et 1 dose de VPI a donné des taux de séroconversion excellents (>99% contre le poliovirus de type 1, 69-78% contre le type 2 et >98% contre le type 3).[91]

Une étude récente au Chili a évalué un calendrier séquentiel prévoyant l'administration d'une dose de VPI à 2 mois, suivie de 2 doses de VPO à 4 et 6 mois. Les taux de séroconversion résultants étaient >98% contre le poliovirus de type 1, > 80% contre le type 2, et >98% contre le type 3 respectivement, ce qui indique une forte immunogénicité de ce calendrier.[92]

Rapport coût/efficacité de l'éradication

Une analyse économique de l'éradication de la poliomyélite en tant que stratégie a reflété la situation programmatique en février 2010, en prenant pleinement en considération les politiques postéradication. Pour l'analyse du rapport coût/efficacité des interventions d'éradication, on a pris en compte les expériences prééradication actuelles et deux politiques futures potentielles distinctes pour la vaccination postéradication. On a utilisé comme référence des comparaisons la vaccination systématique contre la poliomyélite sans les activités spécifiques à l'éradication. On a estimé l'incidence de la poliomyélite à l'aide d'un modèle dynamique de la transmission de l'infection et les coûts à partir des nombres d'enfants vaccinés. En se fondant sur des critères standards, la stratégie d'éradication de la poliomyélite faisant appel au VPOt, puis cessant d'employer

[88] Scientific evidence in support of: Note for the Record: 5th Meeting of the SAGE Working Group, World Health Organization, Geneva, September 3-4, 2012 (http://www.who.int/immunization/sage/meetings/2012/november/3__SAGE_WG_Scientific_Evidence22Oct2012.pdf, accessed February 2016).

[89] Scientific evidence in support of: Note for the Record: 5th Meeting of the SAGE Working Group, World Health Organization, Geneva, September 3–4, 2012 (http://www.who.int/immunization/sage/meetings/2012/november/3__SAGE_WG_Scientific_Evidence22Oct2012.pdf, accessed February 2016).

[90] Grading of scientific evidence – table V: Sequential administration IPV–OPV. Available at http://www.who.int/immunization/polio_sequential_administration_IPV_OPV.pdf, accessed February 2016.

[91] Sutter RW et al. Immunogenicity of a new routine vaccination schedule for global poliomyelitis prevention: an open-label, randomised controlled trial. Lancet 2015. 18 September 2015 (http://dx.doi.org/10.1016/S0140-6736(15)00237-8).

[92] O'Ryan M et al. Inactivated poliovirus vaccine given alone or in a sequential schedule with bivalent oral poliovirus vaccine in Chilean infants: a randomized, controlled, open-label, phase 4, non-inferiority study. Lancet Infect Dis 2015;15:1273–1282.

[88] Scientific evidence in support of: Note for the Record: 5th Meeting of the SAGE Working Group, World Health Organization, Geneva, September 3-4, 2012 (http://www.who.int/immunization/sage/meetings/2012/november/3__SAGE_WG_Scientific_Evidence22Oct2012.pdf, consulté en février 2016.).

[89] Scientific evidence in support of: Note for the Record: 5th Meeting of the SAGE Working Group, World Health Organization, Geneva, September 3-4, 2012 (http://www.who.int/immunization/sage/meetings/2012/november/3__SAGE_WG_Scientific_Evidence22Oct2012.pdf, consulté en février 2016.).

[90] Cotation des preuves scientifiques – tableau V. Sequential administration IPV–OPV. Disponible uniquement en langue anglaise sur http://www.who.int/immunization/polio_sequential_administration_IPV_OPV.pdf, consulté en février 2016.

[91] Sutter RW et al. Immunogenicity of a new routine vaccination schedule for global poliomyelitis prevention: an open-label, randomised controlled trial. Lancet 2015. 18 September 2015 (http://dx.doi.org/10.1016/S0140-6736(15)00237-8).

[92] O'Ryan M et al. Inactivated poliovirus vaccine given alone or in a sequential schedule with bivalent oral poliovirus vaccine in Chilean infants: a randomized, controlled, open-label, phase 4, non-inferiority study. Lancet Infect Dis 2015;15:1273–1282.

Sensitivity analysis suggested that the finding of positive net benefits of the GPEI remained robust over a wide range of assumptions, providing a strong economic justification for polio eradication despite rising costs. Incremental net benefits of polio eradication between 1988 and 2035 were estimated at US$ 40–50 billion (2008 US$; 1988 net present values), with the lower value corresponding to increased adoption of IPV. Despite the high costs of achieving eradication in low-income countries, they account for approximately 85% of the total net benefits generated by the GPEI in the base case analysis.[93]

Country-specific analyses of the incremental cost-effectiveness of switching from tOPV to IPV (in Australia, South Africa and the USA) primarily for VAPP prevention, concluded that changing from tOPV to IPV was not cost effective.[79, 94, 95] Despite the additional cost, those countries nevertheless switched to IPV to avoid the risk of VAPP. The costs of IPV are expected to decrease as global demand increases. A recent analysis of the economics of poliovirus eradication and risk management for 2013–2052 reported approximately US$16 billion in global net benefits (2013 US$) associated with the expected investments of the current strategic plan, coordinated OPV cessation (i.e. OPV2 cessation in 2016, bOPV cessation in 2019), and the polio endgame through 2052.[93]

WHO position

All children worldwide should be fully vaccinated against polio, and every country should seek to achieve and maintain high levels of coverage with polio vaccine in support of the global commitment to eradicate polio.

Indigenous wild poliovirus type 2 has not been detected since 1999. Immunity gaps resulting from insufficient use of tOPV with low vaccination coverage have led to increasing emergence of cVDPVs, with 26%–31% of cases of VAPP associated with the type 2 component in tOPV. It is therefore essential to switch from tOPV (containing type 1, 2 and 3 serotypes) to bOPV (containing only type 1 and 3 serotypes) in national immunization programmes and to coordinate the switch globally. In 2015 the World Health Assembly agreed that all Member States which currently use OPV should prepare for the global withdrawal of the type 2 component of OPV in April 2016.[96] All stocks of tOPV should then be removed and destroyed from service delivery points and their removal confirmed to WHO.

[93] Duintjer Tebbens RJ et al. Economic analysis of the global polio eradication initiative. Vaccine. 2010; 29(2), 334–343.

[94] Griffiths UK et al. The cost-effectiveness of alternate polio immunization policies in South Africa. Vaccine. 2006; 24:5670–5678.

[95] Tucker AW et al. Cost-effectiveness analysis of changing from live oral poliovirus vaccine to inactivated poliovirus vaccine in Australia. Aust N Z J Public Health. 2001; 25(5):411–416.

[96] 68th World Health Assembly, 2015, agenda item 15.2. Poliomyelitis. Available at http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R3-en.pdf, accessed February 2016.

les VPO après l'éradication réussie des PVS a été trouvée d'un très bon rapport coût/efficacité. L'analyse de sensibilité laisse à penser que le résultat attribuant des bénéfices nets positifs à l'IMEP reste solide si l'on fait varier très largement les hypothèses de départ, d'où une forte justification économique pour l'éradication de la poliomyélite malgré la hausse des coûts. Les bénéfices incrémentaux nets de l'éradication de la poliomyélite entre 1988 et 2035 ont été estimés à US$ 40-50 milliards (US$ de 2008; valeurs actuelles nettes en 1988), la valeur basse correspondant à une adoption plus large du VPI. Si les coûts pour obtenir l'éradication de la poliomyélite dans les pays à faible revenu sont élevés, ces pays recueillent aussi environ 85% des bénéfices totaux nets générés par l'IMEP dans l'analyse du cas de base.[93]

Des analyses par pays de l'évolution du rapport coût/efficacité résultant du passage du VPOt au VPI (en Afrique du Sud, en Australie et aux États-Unis) principalement pour prévenir la PPAV, ont conclu que cette transition n'offrait pas un bon rapport coût/efficacité.[79, 94, 95] En dépit du coût supplémentaire, ces pays sont néanmoins passés au VPI pour tenter d'éliminer le risque de PPAV. On s'attend à ce que les coûts du VPI baissent avec l'accroissement de la demande mondiale. Une analyse récente des aspects économiques de l'éradication des poliovirus et de la gestion des risques pour la période 2013-2052 a prévu des bénéfices nets mondiaux à hauteur d'approximativement US$ 16 milliards (US$ de 2013) comme conséquence des investissements attendus du plan stratégique actuel, de l'arrêt coordonné du VPO (c'est-à-dire de l'arrêt du PVO2 en 2016 et de celui du VPOb en 2019) et de la phase finale de l'éradication de la poliomyélite devant se dérouler jusqu'en 2052.[93]

Position de l'OMS

Tous les enfants dans le monde devraient être intégralement vaccinés contre la poliomyélite, et chaque pays devrait s'efforcer d'obtenir et de maintenir des niveaux élevés de couverture par la vaccination antipoliomyélitique à l'appui de l'engagement mondial à éradiquer cette maladie.

Il n'a pas été détecté de poliovirus sauvage autochtone de type 2 depuis 1999. Les lacunes immunitaires résultant de l'utilisation insuffisante du VPOt, s'accompagnant d'une faible couverture vaccinale, ont entraîné un accroissement de l'émergence de PVDVc, avec 26 à 31% des cas de PPAV associés à la composante de type 2 du VPOt. Il est donc essentiel de passer du VPOt (contenant les sérotypes 1, 2 et 3) au VPOb (ne renfermant que les sérotypes 1 et 3) dans les programmes de vaccination nationaux et de coordonner cette transition à l'échelle mondiale. En 2015, l'Assemblée mondiale de la Santé est convenue que tous les États Membres qui utilisent actuellement le vaccin antipoliomyélitique oral devront se préparer au retrait mondial, en avril 2016, de la composante de type 2 du vaccin antipoliomyélitique oral.[96] Tous les stocks de VPOt devront être retirés des points de délivrance et détruits et leur élimination devra être confirmée à l'OMS.

[93] Duintjer Tebbens RJ et al. Economic analysis of the global polio eradication initiative. Vaccine. 2010; 29(2), 334–343.

[94] Griffiths UK et al. The cost-effectiveness of alternate polio immunization policies in South Africa. Vaccine. 2006; 24:5670–5678.

[95] Tucker AW et al. Cost-effectiveness analysis of changing from live oral poliovirus vaccine to inactivated poliovirus vaccine in Australia. Aust N Z J Public Health. 2001; 25(5):411–416.

[96] 68e Assemblée mondiale de la Santé, 2015, point 15.2 de l'ordre du jour. Poliomyélite. Disponible sur http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R3-fr.pdf, consulté en février 2016.

Vaccination with OPV plus IPV

For all countries using OPV in the national immunization programme, WHO continues to recommend the inclusion of at least one dose of IPV in the vaccination schedule. The primary purpose of this IPV dose is to induce an immunity base that could be rapidly boosted should there be an outbreak of polio due to poliovirus type 2 after the removal of type 2 virus from OPV. Additionally, depending on the timing of the administration of the dose or doses of IPV, the inclusion of IPV may reduce risks for the development of VAPP and could boost both humoral and mucosal immunity against poliovirus types 1 and 3 in vaccine recipients.

In polio-endemic countries and in countries at high risk for importation and subsequent spread of poliovirus,[97] WHO recommends a bOPV birth dose (zero dose) followed by a primary series of 3 bOPV doses and at least 1 IPV dose.

The zero dose of bOPV should be administered at birth, or as soon as possible after birth, to maximize seroconversion rates following subsequent doses and to induce mucosal protection before enteric pathogens may interfere with the immune response. Also, a first dose of bOPV given while infants are still protected by maternally-derived antibodies may, at least theoretically, prevent VAPP. Even in cases of perinatal HIV infection, early bOPV vaccination seems to be well tolerated, and no additional risk of VAPP has been documented in such children.

The primary series consisting of 3 bOPV doses plus 1 IPV dose can be initiated from the age of 6 weeks with a minimum interval of 4 weeks between the bOPV doses. If 1 dose of IPV is used, it should be given at 14 weeks of age or later (when maternal antibodies have diminished and immunogenicity is significantly higher) and can be co-administered with a bOPV dose. Programmes may consider alternative schedules based on local epidemiology, including the documented risk of VAPP prior to 4 months of age.

The primary series can be administered according to the regular schedules of national immunization programmes, e.g. at 6, 10, and 14 weeks (bOPV, bOPV, bOPV+IPV), or at 2, 4, and 6 months (bOPV, bOPV+IPV, bOPV or bOPV, bOPV, bOPV+IPV). Both OPV and IPV may be co-administered with other infant vaccines.

For infants starting the routine immunization schedule late (age >3 months) the IPV dose should be administered at the first immunization contact along with bOPV and the other routinely recommended vaccines.

As an alternative to the intramuscular injection of a full dose of IPV, countries may consider using fractional doses (1/5 of the full IPV dose) via the intradermal route, but the programmatic cost and logistic implications of this option should be considered. In the context

[97] The risk of importation and subsequent spread is determined mainly by the level of immunization coverage, sanitation, and overall socioeconomic status.

Vaccination avec le VPO plus le VPI

Pour l'ensemble des pays utilisant le VPO dans leur programme national de vaccination, l'OMS continue de recommander l'inclusion d'au moins une dose de VPI dans le calendrier vaccinal. La finalité première de la dose de VPI est d'induire une base immunitaire qui pourrait rapidement être renforcée en cas de flambée de poliomyélite due à un poliovirus de type 2 après le retrait du VPO du sérotype 2. En outre, selon le moment ou intervient l'administration de la dose ou des doses de VPI, l'introduction du VPI peut réduire les risques de PPAV et pourrait renforcer l'immunité tant humorale que mucosale contre les poliovirus de types 1 et 3 chez les personnes vaccinées.

Dans les pays d'endémie de la poliomyélite et dans ceux très exposés au risque d'importation et de propagation ultérieure de poliovirus,[97] l'OMS préconise une dose de VPO à la naissance (dose zéro), suivie d'une série primaire de 3 doses de VPO et d'au moins 1 dose de VPI.

La dose zéro de VPO devra être administrée à la naissance ou dès que possible après celle-ci pour maximiser les taux de séroconversion avec les doses ultérieures et induire une protection mucosale avant que des agents pathogènes entériques ne puissent interférer avec la réponse immunitaire. De même, l'administration de la première dose de VPO pendant que les nourrissons sont encore protégés par des anticorps d'origine maternelle peut, tout au moins théoriquement, prévenir la PPAV. Même dans les cas d'infection périnatale par le VIH, la vaccination précoce avec le VPO semble bien tolérée et aucun risque supplémentaire n'a été relevé pour ces enfants.

L'administration de la série primaire, composée de 3 doses de VPO plus 1 dose de VPI, peut débuter à l'âge de 6 semaines, avec un intervalle minimum de 4 semaines entre les doses de VPOb. Si l'on utilise une seule dose de VPI, elle devra être administrée à partir de l'âge de 14 semaines (lorsque les anticorps maternels auront baissé et que l'immunogénicité sera notablement plus forte) et elle pourra éventuellement être injectée en même temps que celle de VPOb. Les programmes pourraient envisager d'autres calendriers en fonction de l'épidémiologie locale et notamment du risque observé de PPAV avant l'âge de 4 mois.

La série primaire peut être administrée selon les calendriers habituels des programmes nationaux de vaccination, par exemple à 6, 10 et 14 semaines (VPOb, VPOb, VPOb +VPI) ou à 2, 4 et 6 mois (VPOb, VPOb +VPI, VPOb ou VPOb, VPOb, VPOb+VPI). Le VPO, comme le VPI, peuvent être coadministrés avec d'autres vaccinations infantiles.

Pour les nourrissons débutant tardivement le calendrier de vaccination systématique (à >3 mois), la dose de VPI devra être administrée lors du premier contact vaccinal, en même temps que le VPOb et les autres vaccins systématiquement recommandés.

En tant qu'alternative à l'injection intramusculaire d'une dose complète de VPI, les pays peuvent envisager l'administration de doses fractionnées (1/5 de la dose complète de VPI) par voie intradermique, mais le coût programmatique et les implications logistiques de cette option devront aussi être exami-

[97] Le risque d'importation et de propagation ultérieure est déterminé principalement par le niveau de couverture vaccinale et d'assainissement et par la situation socioéconomique globale.

of an IPV shortage, countries could consider instituting a 2-dose fractional dose schedule which could ensure that all eligible infants receive IPV, is dose-sparing and results in better immunogenicity than a single full dose of IPV. To ensure early protection a schedule of fractional intradermal doses administered at 6 and 14 weeks may be considered. The 2 fractional doses should be separated by a minimum interval of 4 weeks. One fractional-dose IPV may be particularly appropriate for outbreak response if supplies are limited.

In the event that vaccination with IPV cannot be done before the switch from tOPV to bOPV because of supply shortages, catch-up vaccination should be carried out when sufficient supplies become available. Stocks of mOPV2 and IPV are available for outbreak response if a VDPV2 is detected in any country after the withdrawal of tOPV.[98]

The implementation of the new infant schedule (3 bOPV doses + 1 IPV dose) does not replace the need for supplementary immunization activities (SIAs). Those countries with insufficient routine vaccination coverage and which rely on SIAs to increase population immunity should continue the SIAs using bOPV until routine coverage improves or until the globally-coordinated withdrawal of bOPV.

Sequential IPV–OPV schedule

In countries with high vaccination coverage (e.g. 90%–95%) and low importation risk (neighbouring countries and major population movement all having similarly high coverage) an IPV–bOPV sequential schedule can be used when VAPP is a significant concern. Where a sequential IPV–bOPV schedule is used, the initial administration of 1 or 2 doses of IPV should be followed by ≥2 doses of bOPV to ensure both sufficient levels of protection in the intestinal mucosa and a decrease in the burden of VAPP. For sequential IPV–bOPV schedules, WHO recommends that IPV be given at 2 months of age (e.g. a 3-dose IPV–bOPV–bOPV schedule), or at 2 months and 3–4 months of age (e.g. a 4-dose IPV–IPV–OPV–OPV schedule) followed by at least 2 doses of bOPV. Each of the doses in the primary series should be separated by 4–8 weeks depending on the risk of exposure to poliovirus in early childhood.

IPV-only schedule

An IPV-only schedule may be considered in countries with sustained high vaccination coverage and very low risk of both WPV importation and transmission. IPV is usually given by intramuscular injection as it is less reactogenic than when given by subcutaneous injection, and it may be included as a component of combination vaccines. A primary series of 3 doses of IPV should be administered beginning at 2 months of age. If the primary series begins earlier (e.g. with a 6, 10 and

[98] No. 50, 2015, pp. 681–700.

nés. Dans le contexte d'une pénurie de VPI, les pays devront envisage de mettre en place un calendrier comprenant 2 doses fractionnées, qui permettrait de garantir que tous les nourrissons répondant aux critères pour recevoir le VPI bénéficient de ce vaccin, de réaliser des économies de doses et d'obtenir une meilleure immunogénicité qu'une dose unique complète de VPI. Pour assurer une protection précoce, on peut envisager l'administration d'un calendrier composé de doses fractionnées à 6 et 14 semaines. Les deux doses fractionnées devront être séparées d'un intervalle minimum de 4 semaines. Le VPI sous forme de dose fractionnée intradermique unique peut être tout particulièrement adapté à la réponse à une flambée si les approvisionnements sont limités.

Dans les cas où la vaccination avec le VPI ne peut être effectuée avant le passage du VPOT au VPOb en raison d'une pénurie de vaccins, des vaccinations de rattrapage devront être pratiquées lorsque des approvisionnements suffisants seront disponibles. Des stocks de VPOm2 et de VPI sont à disposition pour répondre aux flambées en cas de détection d'un PVDV2 dans un pays quelconque après le retrait du VPOt.[98]

La mise en œuvre d'un nouveau calendrier infantile (3 doses de VPOb + 1 dose de VPI) n'élimine pas la nécessité d'activités de vaccination supplémentaires (AVS). Les pays dont la couverture par la vaccination systématique est insuffisante et qui s'appuient sur des AVS pour accroître l'immunité de leur population devront poursuivre ces AVS avec le VPOb jusqu'à ce que la couverture par la vaccination systématique s'améliore ou jusqu'au retrait coordonné à l'échelle mondiale du VPOb.

Calendrier séquentiel VPI-VPO

Dans les pays bénéficiant d'une forte couverture vaccinale (90-95%, par exemple) et où le risque d'importation est faible (avec des pays limitrophes et des populations déplacées importantes présentant également des taux de couverture élevés), un calendrier séquentiel VPI-VPOb peut être appliqué si les PPAV représentent une préoccupation importante. Lorsqu'on utilise un tel calendrier, l'administration initiale de 1 ou 2 doses de VPI doit être suivie de celle de ≥2 doses de VPOb pour garantir un niveau suffisant de protection de la muqueuse intestinale et une diminution acceptable de la charge de PPAV. Pour les calendriers séquentiels VPI-VPOb, l'OMS préconise d'administrer le VPI à l'âge de 2 mois (calendrier en 3 doses VPI-VPOb-VPOb, par exemple) ou à 2 mois et à 3-4 mois (calendrier en 4 doses VPI-VPI-VPO-VPO, par exemple), puis au moins 2 doses de VPOb. Entre les différentes doses de la série primaire, il faut prévoir un intervalle de 4-8 semaines selon le risque d'exposition au poliovirus dans la petite enfance.

Calendrier «tout VPI»

Il est possible d'envisager un calendrier «tout VPI» dans les pays où la couverture vaccinale est durablement forte et où le risque d'importation et de transmission de PVS est très bas. Le VPI est habituellement administré par voie intramusculaire car il est ainsi moins réactogène qu'en injection sous-cutanée et peut entrer dans la composition d'un vaccin combiné. On administrera une série primaire de 3 doses de VPI en commençant à 2 mois. Si la série primaire débute plus tôt (calendrier d'administration à 6, 10 et 14 semaines, par exemple), il faudra

[98] N° 50, 2015, pp. 681-700.

14-week schedule) then a booster dose should be given after an interval of ≥6 months (for a 4-dose schedule).

Switching to sequential schedules or exclusive use of IPV

To mitigate the risk of undetected transmission, WHO recommends that endemic countries and countries with a high risk of WPV importation[99] should not switch to an IPV-only or a sequential IPV–bOPV schedule at this time. The 3 bOPV+1 IPV schedule as currently recommended should be adopted and SIAs should continue to support intensive efforts to eliminate poliovirus transmission. A sequential IPV–bOPV schedule or IPV-only schedule can be considered in order to minimize the risk of VAPP, but only after a thorough review of local epidemiology.

Special populations, contraindications and precautions

Polio vaccine (IPV or bOPV) may be administered safely to asymptomatic HIV-infected infants. HIV testing is not a prerequisite for vaccination.

bOPV is contraindicated in severely immunocompromised patients with known underlying conditions such as primary immunodeficiencies, disorders of the thymus, symptomatic HIV infection or low CD4 T-cell values,[100] malignant neoplasm treated with chemotherapy, recent haematopoietic stem cell transplantation, drugs with known immunosuppressive or immunomodulatory properties (e.g. high dose systemic corticosteroids, alkylating drugs, antimetabolites, TNF-α inhibitors, IL-1 blocking agent, or other monoclonal antibodies targeting immune cells), and current or recent radiation therapies targeting immune cells. These populations can safely receive IPV.

Co-administration with other vaccines

IPV and bOPV may be administered concurrently and both can be given together with other vaccines.

Vaccination of travellers

Before travelling abroad, persons residing in countries with active transmission of a wild or vaccine-derived poliovirus should have completed a full course of polio vaccination in compliance with the national schedule, and received one dose of IPV or bOPV within 4 weeks to 12 months of travel, in order to boost intestinal mucosal immunity and reduce the risk of poliovirus shedding. Some polio-free countries may require resident travellers from polio-infected countries to be vaccinated against polio in order to obtain an entry visa, or they may require that travellers receive an additional dose on arrival, or both. Travellers to infected

[99] Potential for importation is considered very high in countries bordering endemic countries or countries that have recurrent outbreaks; the potential is considered high if there is a history of importation plus high traffic across the border; the potential is considered moderate in the rest of the world.

[100] <15% (or <750 for infants <12 months, <500 for those 1 through 5 years and <200 for those ≥6 years).

injecter une dose de rappel à l'issue d'un intervalle de ≥6 mois (pour un calendrier en 4 doses).

Passage à un calendrier séquentiel ou tout VPI

Pour diminuer le risque de transmission non détectée, l'OMS recommande aux pays d'endémie ou exposés à un risque conséquent d'importation de PVS[99] de ne pas passer à un calendrier «tout VPI» ou séquentiel VPI-VPOb pour l'instant. Ils devront adopter le calendrier 3 VPOb + VPI actuellement recommandé et poursuivre les AVS en vue d'appuyer les efforts intensifs pour éliminer la transmission des poliovirus. Un calendrier séquentiel VPI-VPOb ou «tout VPI» peut être envisagé pour minimiser le risque de PPAV, mais seulement après un examen approfondi de l'épidémiologie locale.

Populations particulières, contre-indications et précautions

Le vaccin antipoliomyélitique (VPI ou VPO) peut être administré sans risque à des nourrissons infectés par le VIH asymptomatiques. Le dépistage du VIH n'est pas un prérequis pour la vaccination.

Le VPOb est contre-indiqué chez les patients sévèrement immunodéprimés présentant des pathologies sous-jacentes connues telles que déficit immunitaire primaire, troubles thymiques, infection à VIH symptomatique ou faible numération des lymphocytes T CD4,[100] néoplasme malin traité par chimiothérapie, greffe récente de cellules-souches hématopoïétiques, prise de médicaments ayant des propriétés immunosuppressives ou immunomodulatoires connues (corticoïdes à haute dose par voie systémique, agents alkylants, antimétabolites, inhibiteurs du TNF-α, agent bloquant l'IL-1 ou autres anticorps monoclonaux ciblant les cellules immunitaires), ou encore radiothérapie en cours ou récente visant des cellules immunitaires. Ces populations peuvent recevoir sans risque le VPI.

Coadministration avec d'autres vaccins

Le VPI et le VPOb peuvent être injectés simultanément et l'un comme l'autre peuvent être administrés en association avec les autres vaccins.

Vaccination des voyageurs

Avant de se rendre à l'étranger, les personnes résidant dans des pays où s'opère la transmission active de poliovirus sauvages ou dérivés d'une souche vaccinale devront avoir reçu une série complète de vaccinations antipoliomyélitiques en conformité avec le calendrier national, ainsi qu'une dose de VPI ou de VPOb dans les 4 semaines à 12 mois précédant le voyage, afin de renforcer l'immunité mucosale intestinale et de réduire le risque d'excrétion de poliovirus. Certains pays exempts de poliomyélite peuvent exiger des voyageurs en provenance de pays infectés par cette maladie dans lesquels ils résident, qu'ils soient vaccinés contre elle pour obtenir un visa d'entrée ou qu'ils reçoivent une dose supplémentaire en arrivant, voire imposer

[99] Le potentiel d'importation est considéré comme très important dans les pays limitrophes des pays d'endémie qui subissent des flambées récurrentes; comme important en présence d'antécédents d'importation et d'un trafic dense à travers la frontière; et comme moyen dans le reste du monde.

[100] <15% (ou <750 chez les nourrissons <12 mois, <500 chez les enfants de 1 à 5 ans et <200 chez ceux de ≥6 ans).

areas should be vaccinated according to their national schedules.

Vaccination of health-care workers

All health-care workers worldwide should have completed a full course of primary vaccination against poliomyelitis. ■

l'une et l'autre conditions. Les voyageurs à destination des zones touchées devront être vaccinés conformément à leur calendrier national.

Vaccination du personnel soignant

Tous les soignants dans le monde devront avoir reçu une série complète de doses de primovaccination contre la poliomyélite. ■

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/topics/infectious_diseases/en/**	Programmes d'éradication/élimination
Fact sheets on infectious diseases	**http://www.who.int/topics/infectious_diseases/factsheets/en/**	Aide-mémoires sur les maladies infectieuses
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
Human African trypanosomiasis	**http://www.who.int/trypanosomiasis_african/en/**	Trypanosomiase humaine africaine
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
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/**	Filariose 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	**http://www.who.int/rabies/en**	Rage
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
Soil-transmitted helminthiases	**http://www.who.int/intestinal_worms/en/**	Géohelminthiases
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 discussion and statement in relation with the IPV supply situation

10 March 2016

BACKGROUND

In February and March 2016, the two main IPV suppliers (i.e. Bilthoven Biologicals and Sanofi Pasteur) informed WHO/UNICEF that they will substantially reduce or delay the quantities of IPV supplied in 2016 and 2017, due to technical challenges in scaling up IPV bulk production and the associated quality control testing and releases. This has created significant delays in IPV introduction and shortages of supply in many countries.

SAGE POLIO WG DISCUSIONS

The SAGE WG closely reviewed the IPV supply situation during a conference call held on 3 March 2016 as well as via email in response to the further details provided on 7 March 2016.

While the SAGE WG expressed concern that the shortage may cause serious disruption in many countries, it unanimously reaffirmed that the public health risks associated with the continued use of the type 2 component contained in tOPV outweigh the risks of new VDPV2 emergence after the global withdrawal of OPV type 2, even in countries where IPV introduction will be further delayed. It furthermore noted that a global stockpile of mOPV2 is available for emergency response in case of cVDPV2 emergence.

It reaffirmed that countries should proceed with the switch as scheduled during the period 17 April to 1 May 2016.

The SAGE WG also reviewed evidence available on the administration of fractional, intradermal (ID) IPV. Recent studies from Bangladesh[1] and Cuba[2] demonstrate that the immunogenicity of two fractional doses of IPV (0.1 ml) administered through the intra dermal route are superior to one full dose (0.5 ml) administered through the intra muscular route. In Cuba, two fractional doses of IPV given intradermally at 4 and 8 month induced 98% seroconversion rate against type 2, in comparison to 63% seroconversion conferred by one full dose administered intra-muscularly at 4 months. Similarly, in Bangladesh, two fractional doses of IPV administered intradermally at 6 and 14 weeks in induced 81% seroconversion against type 2 versus 39% with one full dose of IPV administered intra-muscularly at 6 weeks. The seroconversion rate reported following two fractional doses at 6 and 14 weeks (i.e. 81%) in Bangladesh is higher than the seroconversion following one full dose of IPV given at 14 weeks (73%) reported from a subsequent trial, conducted by the same investigators, in a similar study population in Bangladesh, using the same laboratory (Anand A. Unpublished data, 2016). In both studies, two fractional doses induced substantially higher antibody titres (16- to 32-fold higher) against type 2 than one full dose (and two fractional doses at 6 and 14 weeks in Bangladesh induced higher antibody titres than one full dose at 14 weeks in the follow-on study [10-fold higher]). The WG concluded that the proposed schedule of two fractional IPV doses can induce equal or better immunity than the one full-dose schedule.

Related developments

Based on these data and ongoing IPV shortage, the updated WHO position paper on polio vaccine (to be published on 25 March 2016) reaffirmed the previously stated potential alternative of using a fractional dose of IPV via the ID route and states that, in order to ensure that all eligible infants receive IPV, countries could consider instituting a 2-dose fractional dose schedule which is dose-sparing and results in better immunogenicity than a single full dose of IPV.

In March 2016, the India Expert Advisory Group (IEAG) recommended to the Ministry of Health and Family Welfare that 6-7 states in India should introduce a schedule of two fractional doses of IPV to be administered at 6 and 14 weeks of age[3].

SAGE Position

During its 2nd preparatory teleconference for the April SAGE meeting, SAGE discussed the above.
SAGE fully concurs with the WG conclusions:

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[1] Anand A et al. Early priming with inactivated poliovirus vaccine (IPV) and intradermal fractional dose IPV administered by a microneedle device: A randomized controlled trial. Vaccine. 2015 27;33:6816-22

[2] Resik S et al. Priming after a fractional dose of inactivated poliovirus vaccine. N Engl J Med 2013;368: 416-24.

[3] India Expert Advisory Group for Polio Eradication. Delhi, India, 26 February 2016. Conclusion and Recommendations http://www.who.int/immunization/diseases/poliomyelitis/endgame_objective2/inactivated_polio_vaccine/planning/en/

- SAGE re-affirms its October 2015 conclusion that the Switch should proceed in April 2016, even with the recent decline in IPV supply
- SAGE recommends that countries consider adopting a two fractional doses IPV schedule (e.g. at 6 and 14 weeks for early protection), as mentioned in the upcoming WHO Polio Position Paper
- SAGE recommends that countries which are considering introducing a fractional dose schedule should ensure that health workers capacity to administer ID injection is assessed and strengthened.

Vaccine 33 (2015) 6816–6822

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Early priming with inactivated poliovirus vaccine (IPV) and intradermal fractional dose IPV administered by a microneedle device: A randomized controlled trial

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ARTICLE INFO

Article history:
Received 23 August 2015
Received in revised form
14 September 2015
Accepted 15 September 2015
Available online 23 October 2015

Keywords:
Oral polio vaccine
Inactivated polio vaccine
Priming
Polio immunogenicity

ABSTRACT

Introduction: Inactivated poliovirus vaccine (IPV) introduction and phased oral poliovirus vaccine (OPV) cessation are essential for eradication of polio.
Methods: Healthy 6-week old infants in Bangladesh were randomized to one of five study arms: receipt of trivalent OPV (tOPV) or bivalent OPV (bOPV) at ages 6, 10 and 14 weeks, intramuscular IPV or intradermal one-fifth fractional dose IPV (f-IPV) at ages 6 and 14 weeks, or f-IPV at ages 6 and 14 weeks with bOPV at age 10 weeks (f-IPV/bOPV). All participants received tOPV at age 18 weeks.
Results: Of 975 infants randomized, 95% (922) completed follow-up. Type 1 seroconversion after 3 doses at 6, 10 and 14 weeks was higher with bOPV compared with tOPV (99% vs 94%, $p = 0.019$). Seroconversions to types 1 and 3 after 2 IPV doses at ages 6 and 14 weeks were no different than after 3 doses of tOPV or bOPV at ages 6, 10 and 14 weeks. A priming response, seroconversion 1 week after IPV at 14 weeks among those who did not seroconvert after IPV at 6 weeks, was observed against poliovirus types 1, 2 and 3 in 91%, 84% and 97%, respectively. Compared with IPV, f-IPV failed non-inferiority tests for seroconversion with 1 or 2 doses and priming after 1 dose.
Discussion: The findings demonstrate considerable priming with IPV at age 6 weeks, comparable immunogenicity of tOPV and bOPV, and inferior immunogenicity of one-fifth f-IPV compared with IPV. If IPV induced priming at age 6 weeks is similar to that at age 14 weeks, IPV could be administered at a younger age and possibly with a higher coverage.

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1. Introduction

Oral poliovirus vaccines (OPV) consist of live attenuated poliovirus strains that can revert and cause paralysis, that is indistinguishable from paralysis caused by wild polioviruses (WPV), either due to vaccine-associated paralytic polio (VAPP) or circulating vaccine-derived polioviruses (cVDPV), in which the reverted vaccine virus also acquires the ability to circulate [1]. Since the last type 2 WPV (WPV2) was reported in 1999 in India [2] and about 87% of VDPVs during 2000–2013 were type 2 [3], the strategic advisory group of experts on immunization (SAGE) has recommended a phased cessation of OPV starting with type 2 OPV [4]. In countries using trivalent OPV (tOPV), a mixture of types 1, 2 and 3 OPV, in routine immunization (RI), SAGE has recommended a switch to bivalent OPV (bOPV), a mixture of OPV types 1 and 3 following introduction of 1 dose of inactivated poliovirus vaccine (IPV) generally at age ≥14 weeks [5]. It is expected that delaying IPV administration to age ≥14 weeks is likely to maximize IPV immunogenicity [5]; however, compared with vaccinating at age 6 weeks, vaccination at age ≥14 weeks is likely to be associated with lower vaccination coverage in some high-risk countries [6].

The principal objective of introducing IPV with bOPV is to mitigate the risk associated with increased susceptibility to WPV2 or cVDPV2. For IPV, priming is defined as a seroconversion response

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http://dx.doi.org/10.1016/j.vaccine.2015.09.039
0264-410X/Published by Elsevier Ltd.

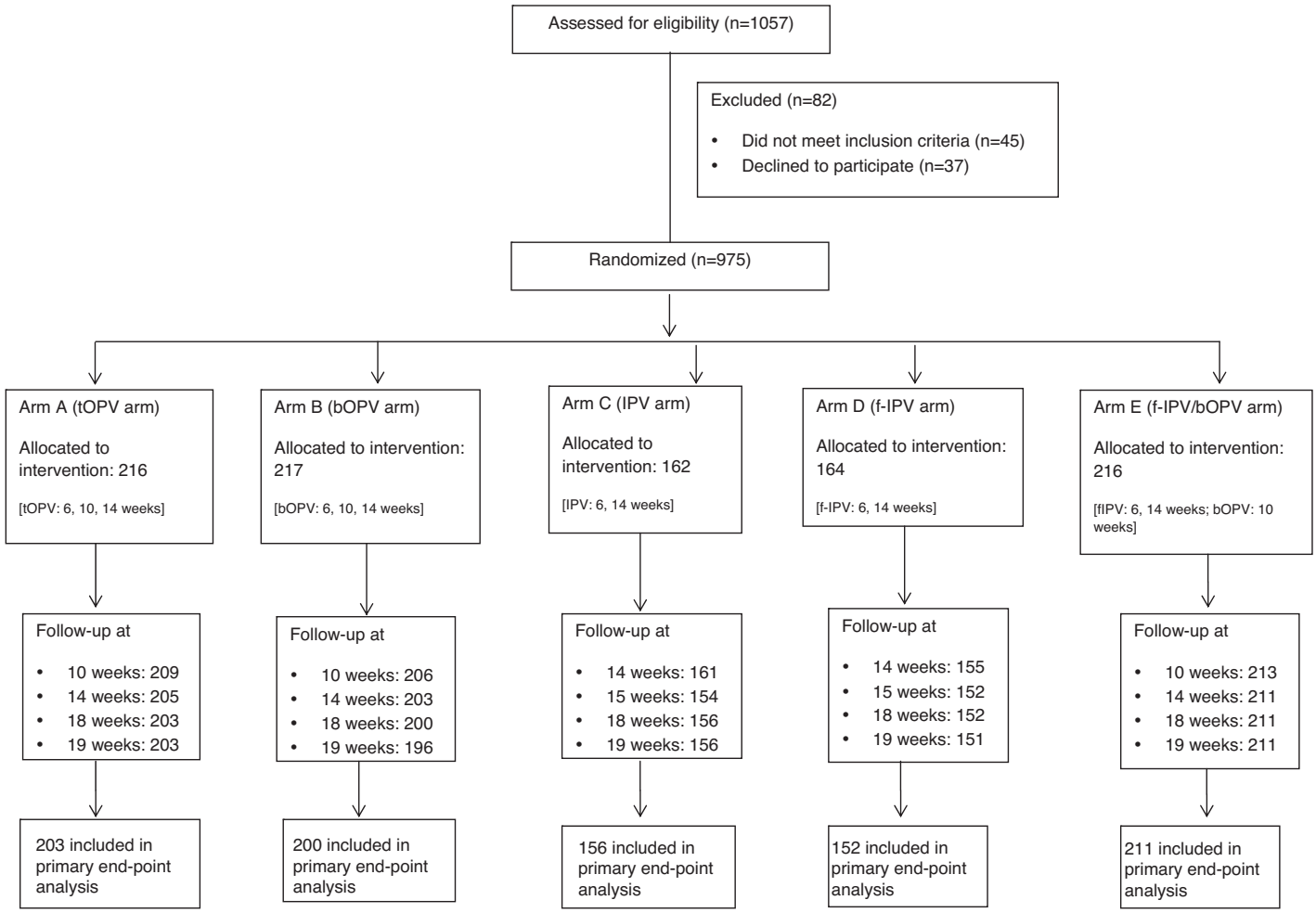

Fig. 1. Trial profile with number of subjects followed by study time-point.

1 week after a second dose of IPV among those who did not seroconvert after the first IPV dose. One clinical trial in Cuba reported considerable immunogenicity (seroconversion [63%] and priming [35%]) with 1 dose of IPV at age 4 months [7]. The absence of immunogenicity data by age, including priming response after IPV, is the chief limitation in assessing the optimal age for IPV administration in RI. In 2012, SAGE also recommended collecting additional immunogenicity data on intradermal (ID) one-fifth dose of IPV (0.1 ml fractional IPV [f-IPV]) as a potential substitute for intramuscular IPV (0.5 ml) [8].

2. Methods

2.1. Randomization and masking

We conducted an open-label 5-arm randomized controlled trial from 27 November 2012 to 30 November 2013 in Mirpur, an urban neighborhood in Dhaka, Bangladesh. The trial enrolled participants from 5 different sections of Mirpur. During the duration of the trial no polio vaccination campaigns were conducted in or around the study site. Infants were assigned randomly to one of five arms using a block randomization scheme of 65 blocks with a block size of 18 and an allocation ratio of 4:4:3:3:4 (Fig. 1). The tOPV arm received tOPV at ages 6, 10 and 14 weeks; the bOPV arm received bOPV at ages 6, 10 and 14 weeks; the IPV arm received IPV at ages 6 and 14 weeks; the f-IPV arm received f-IPV at ages 6 and 14 weeks; and the f-IPV/bOPV arm received f-IPV at ages 6 and 14 weeks with bOPV at age 10 weeks. All participants received tOPV at age 18 weeks (Table 1 in Supplementary Appendix).

2.2. Study objectives

The study's three primary objectives were to compare immunogenicity of (1) f-IPV and bOPV with bOPV alone; (2) 3 doses of tOPV with 3 doses of bOPV; and (3) 2 doses of intramuscular IPV with 2 doses of f-IPV.

2.3. Study design and procedures

Infants were recruited at age 6–7 weeks (42–51 days), if the parents were willing to participate, comply with study procedures, and provide written informed consent. Exclusion criteria included (1) receipt of any polio vaccine before enrollment; (2) diagnosis or suspicion of immunodeficiency or a bleeding disorder; (3) known allergy to polio vaccines or constituents; (4) any acute illness such as vomiting, diarrhea or infection immediately before enrollment; and (5) an infant who was part of a multiple birth. Enrolled participants were withdrawn from the study if requested by their parents or if they received polio vaccine outside of the study.

Study physicians administered all study vaccines and routine non-polio vaccines for infants as recommended by the Bangladesh Ministry of Health and Family Welfare. Intramuscular IPV (0.5 ml) was administered using a standard needle and syringe. Intradermal f-IPV (0.1 ml) was administered using NanoPass MicronJet 600

(MJ600), a microneedle device with three microneedles (0.6 mm in length) that attaches to an intradermal syringe. Multiple clinical trials have been conducted using MJ600 [9–12]. IPV and f-IPV were administered in the anterolateral thigh, opposite the side used for routine immunization of injectable vaccines.

Blood samples (1 ml) were obtained by venipuncture at ages 6, 14, and 18 weeks from all participants and at age 15 weeks from participants assigned to IPV or f-IPV arms before administering any scheduled study vaccine. Sera were stored at −20 °C and tested for antibodies to poliovirus types 1, 2 and 3 at the Centers for Disease Control and Prevention (CDC), Atlanta, USA using microneutralization assay. Titers below a dilution of 1:8 were considered negative for presence of poliovirus antibodies and the highest measurable titer was 1:1448. Parents were asked to collect a stool specimen (8 g) from participants 1 week after tOPV administration at age 18 weeks. Stool specimens were stored at −20 °C and tested at CDC for presence of poliovirus by type [13].

2.4. Analysis

No published studies were found to have administered f-IPV with bOPV, or 3 doses of bOPV. Therefore, for sample size calculations based on limited evidence, we assumed seroconversions of 85% for types 1 and 3 with f-IPV and bOPV and 95% with 3 doses of bOPV [14,15]. For tOPV, we assumed sero-conversions of 75% for type 1 and 65% for type 3 [16]. Therefore, a sample size of 207 per arm would be sufficient to obtain a power of 90% with two-sided α of 0.05 to detect a difference in seroconversion of at least 10% when comparing 3 doses of bOPV with 3 doses of tOPV, and 2 doses of f-IPV and 1 dose of bOPV with 3 doses of bOPV. No published studies were found to have reported immunogenicity of IPV or f-IPV with two doses 8 weeks apart at ages 6 and 14 weeks. For a non-inferiority comparison, we assumed a sero-conversion of 90% with both IPV and f-IPV with a non-inferiority margin of 10% [14,17]. For this comparison a sample size of 155 per arm is required for a power of 90% with one-sided α of 0.05. Hence, the effective sample size for the trial was 931, with an enrollment target of 1170 assuming 20% attrition (Table 1 in Supplementary Appendix).

Seroconversion was defined as either conversion from seronegative to seropositive or a four-fold increase in antibody titers between two specimens after adjusting for decay of maternal antibodies. The half-life of maternal antibodies was assumed to be 28 days [14,18]. The primary analytical approach was intent-to-treat for participants with serological results. The primary end-point was seroconversion at age 18 weeks. To compare immunogenicity across study arms, the proportion of participants who seroconverted were compared using Fisher's exact test (two-tailed). Priming was defined as a seroconversion response at age 15 weeks after receipt of the second IPV/f-IPV dose among those who did not seroconvert by age 14 weeks after one IPV/f-IPV dose at age 6 weeks. Reverse cumulative distribution curves, which are constructed by representing on the vertical axis the percent of subjects with antibody titers equal to or greater than that marked in x-axis, were used to compare distribution of antibody titers by study arms [19].

2.5. Study oversight

The study protocol was reviewed by icddr,b's Institutional Review Board (IRB). The study was conducted in compliance with good clinical practice guidelines. UNICEF assisted in the procurement of vaccines used in this study. OPV was manufactured by Sanofi Pasteur and IPV was manufactured by the Netherlands Vaccine Institute (NVI). NanoPass Technologies Ltd. donated the supplies of MJ600. UNICEF, Sanofi Pasteur, NanoPass, and NVI had no role in the study design, implementation, data analysis, or interpretation of study results. The study was registered with Clinicaltrials.gov (NCT01813604). Adverse events data were reviewed by the Data Safety Monitoring Board (DSMB) of icddr,b.

2.6. Role of funding source

The study was funded by the Global Immunization Division of the Centers for Disease Control and Prevention. CDC staff participated in the study design, sample testing, data analysis and decision to submit for publication.

3. Results

3.1. Baseline characteristics

The study enrolled and randomized 975 participants and of these, 922 (95%) with blood specimens available at ages 6 and 18 weeks were included in the primary end-point analysis (Fig. 1). Enrollment was stopped after enrolling 975 participants as the study had achieved its effective sample size due to lower than anticipated study attrition. No statistically significant differences were observed at baseline among participants who completed the study compared with those who did not (data not shown) except that median type 2 antibody titers at baseline were lower for those who completed the study (1:28 vs 1:41, Kruskal–Wallis = 0.036). No other significant differences in baseline characteristics, including seroprevalence to polioviruses, were observed among study arms (Table 1).

3.2. Humoral immunogenicity

The median bleb diameter after intradermal injection with MJ600 was 10 mm and 99% of the participants had no residual liquid present on the skin following the injection.

Seroconversion to poliovirus type 1 (PV1) after 2 and 3 doses was higher in the bOPV arm compared with the tOPV arm (2 doses: 93% vs 87%, $p = 0.047$; 3 doses: 99% vs 94%, $p = 0.019$; Table 2). PV1 seroconversion with 2 doses of IPV (95%) was statistically no different from that observed with 3 doses of tOPV or bOPV. PV1 seroconversion with 2 doses of f-IPV and 1 dose of bOPV was higher than that observed with 2 doses of f-IPV alone ($p = 0.005$) and no different from that with 3 doses of tOPV or bOPV.

Seroconversion at 18 weeks to PV2 was higher with 3 doses of tOPV compared with 2 doses of IPV $p = 0.002$) or f-IPV in either f-IPV arms ($p < 0.001$). Seroconversion to PV3 was statistically no different with 3 doses of tOPV (95%) compared with 3 doses of bOPV (94%), 2 doses of IPV (97%) or f-IPV (89%), or 2 doses of f-IPV with 1 dose of bOPV (94%).

Compared with IPV, f-IPV failed the non-inferiority test for all serotypes for seroconversion observed with 1 or 2 doses (Fig. 2). Additionally, compared with IPV, f-IPV failed the non-inferiority test for all serotypes for priming response observed at 15 weeks.

Reverse cumulative distribution curves for antibody titers by study arm at age 18 weeks show that the highest titers were reached for PV1 in the bOPV arm, PV2 in the tOPV arm and PV3 in the IPV arm (Fig. 3). f-IPV was associated with the lowest titers for all three poliovirus types among those receiving type specific vaccines. One dose of IPV or f-IPV was not associated with a substantial change in distribution of antibody titers, despite the high degree of priming with 1 dose; however, within a week of the second dose of IPV or f-IPV, a rapid rise in antibody titers was observed (Fig. 1 in Supplementary Appendix).

3.3. Intestinal mucosal immunity

One week after receiving tOPV at age 18 weeks, 15%, 6%, and 8% of participants in the tOPV arm were excreting PV 1, 2, and

Table 1
Baseline characteristics among those who completed the study by study arms.

Baseline characteristics	A tOPV ($n=203$)		B bOPV ($n=200$)		C IPV ($n=156$)		D f-IPV ($n=152$)		E f-IPV/bOPV ($n=211$)		p-value[a]
Median age in days (range)	44 (41, 53)		44 (41, 53)		44 (42, 53)		44 (41, 52)		44 (41, 53)		0.662
Male n (%)	95	46.8%	99	49.5%	79	50.6%	79	52.0%	110	52.1%	0.828
Mother's education n (%)											
No formal school	36	17.7%	27	13.5%	29	18.6%	24	15.8%	40	19.0%	
Primary school	88	43.4%	92	46.0%	68	43.6%	70	46.1%	87	41.2%	0.869
Middle school	36	17.7%	42	21.0%	30	19.2%	25	16.5%	49	23.2%	
High school	33	16.3%	34	17.0%	27	17.3%	28	18.4%	32	15.2%	
Graduate	10	4.9%	5	2.5%	2	1.3%	5	3.3%	3	1.4%	
Type 1 seroprevalence											
n (%)	99	48.8%	97	48.5%	78	50.0%	77	50.7%	100	47.4%	0.976
Median (range)[b]	28 (9, 1448)		18 (9, 1448)		23 (9, 1448)		23 (6, 1448)		23 (9, 724)		0.947
Type 2 seroprevalence											
n (%)	118	58.1%	118	59.0%	95	60.9%	82	54.0%	124	58.8%	0.796
Median (range)[b]	28 (9, 1448)		36 (9, 1448)		28 (9, 1448)		28 (9, 1448)		23 (9, 1448)		0.884
Type 3 seroprevalence											
n (%)	51	25.1%	56	28.0%	43	27.6%	38	25.0%	65	30.8%	0.698
Median (range)[b]	23 (9, 1448)		23 (9, 1024)		23 (9, 1448)		18 (9, 362)		18 (9, 1448)		0.643
Wasting present n (%)	31	15.3%	38	19.0%	28	18.0%	33	21.7%	34	16.1%	0.545
Stunting present n (%)	40	19.7%	37	18.5%	28	18.0%	31	20.4%	50	23.7%	0.661
Exclusive breastfeeding n (%)	180	88.7%	170	85.0%	134	85.9%	130	85.5%	175	82.9%	0.465

tOPV, trivalent oral poliovirus vaccine (OPV); bOPV, bivalent OPV; IPV, inactivated poliovirus vaccine; f-IPV, fractional IPV.
[a] Fisher's exact test. Kruskal–Wallis test used for mother's education and rank test for medians.
[b] Among those with titers ≥8.

Fig. 2. Differences in seroconversion and priming between fractional intradermal inactivated poliovirus vaccine (f-IPV) arm and intramuscular IPV arm by poliovirus type. f-IPV fails to pass the test of non-inferiority if the lower limit of the 90% confidence interval crosses −10%.

3, respectively (Table 2). Among participants in the bOPV arm, 61% were excreting PV2 1 week after receiving tOPV. The percent of participants excreting type 1 poliovirus was statistically lower in the bOPV arm compared with the f-IPV/bOPV arm (4% vs 13%, Fischer's exact = 0.001). The percent excreting PV3 was statistically lower in the bOPV arm compared with f-IPV/bOPV arm (6% vs 14%, Fischer's exact = 0.013). No statistically significant differences in percent excreting polioviruses by type were observed between IPV and f-IPV arms.

3.4. Adverse events

No adverse events (AE) were reported among participants 30 min after receiving the study vaccine. During follow-up (age 6–19 weeks), 68 AE were reported among participants; 11 were considered serious AE (SAE), including hospitalization or death (Table 2 in Supplementary Appendix). Three infants died during follow-up: two in the sequential f-IPV/bOPV arm and one in the f-IPV arm. No AE/SAE were attributed to trial vaccines or MJ600 by the DSMB.

4. Discussion

The study demonstrated that considerable priming can be achieved with 1 dose of IPV at age 6 weeks. Cumulatively, 90% of children had either seroconverted or were primed against type 2 poliovirus with 1 dose of IPV at age 6 weeks. These results are particularly relevant for current policy considerations regarding global polio eradication. In November 2013, SAGE recommended introduction of at least 1 dose of IPV at age ≥14 weeks in RI in countries where IPV has not been introduced, in advance of a global implementation of the switch from tOPV to bOPV. With removal of type 2 OPV, the objective of IPV introduction is to maximize type 2 population immunity, which is a product of IPV immunogenicity and coverage. If the considerable priming noted in this study at age 6 weeks is similar to the priming noted at age 14 weeks, IPV vaccination at age 6 weeks will likely lead to higher population immunity compared with vaccination at age 14 weeks

Table 2
Humoral and intestinal immunogenicity by study arm.

	A tOPV		B bOPV		C IPV*		D f-IPV*		E f-IPV/bOPV		Fisher's exact test (a priori)	Fisher's exact test (post hoc)**
Type 1												
Seroconversion by 14 weeks: *n* (%)	178/205	86.8%[b,e]	189/203	93.1%[a,b,f]	57/161	35.4%[e,f]	20/155	12.9%[c,d,f]	173/211	82.0%[a,d]	[a] $p = 0.001$ B vs E; [b] $p = 0.047$ A vs B; [c] $p < 0.001$ A vs D; [d] $p < 0.001$ D vs E; NS: A vs E	[e] $p < 0.001$ A vs C; [f] $p < 0.001$ B vs C
Priming response by 15 weeks: *n* (%)†	–	–	–	–	78/86	90.7%	91/109	83.5%	–	–		
Cumulative effect of one dose (seroconversion and priming): *n* (%)†	–	–	–	–	124/132	93.9%	110/128	85.9%	–	–		
Seroconversion by 18 weeks: *n* (%)	190/203	93.6%[a]	197/200	98.5%[a]	148/156	94.9%	133/152	87.5%[b]	202/211	95.7%[b]	[a] $p = 0.019$ A vs B; [b] $p = 0.005$ D vs E; NS: B vs E; A vs E; A vs D	NS: A vs C; B vs C
Poliovirus shedding at 19 weeks: *n* (%)	31/203	15.3%	7/196	3.6%[a]	77/156	49.4%	73/151	48.3%	28/211	13.3%[a]	[a] $p = 0.001$ B vs E; NS: C vs D	
Type 2												
Seroconversion by 14 weeks: *n* (%)	190/205	92.7%[b,c,d,e]	14/203	6.9%[a,b,f]	62/161	38.5%[e,f]	30/155	19.4%[d]	53/211	25.1%[a,c]	[a] $p < 0.001$ B vs E; [b] $p < 0.001$ A vs B; [c] $p < 0.001$ A vs E; [d] $p < 0.001$ A vs D; NS: D vs E	[e] $p < 0.001$ A vs C; [f] $p < 0.001$ B vs C
Priming response by 15 weeks: *n* (%)†	–	–	–	–	66/79	83.5%	73/101	72.3%	–	–		
Cumulative effect of one dose (seroconversion and priming): *n* (%)†	–	–	–	–	119/132	90.2%	100/128	78.1%	–	–		
Seroconversion by 18 weeks: *n* (%)	200/203	98.5%[b,c,d,e]	28/200	14%[a,b,f]	142/156	91%[e,f]	123/152	80.9%[d]	172/211	81.5%[a,c]	[a] $p < 0.001$ B vs E; [b] $p < 0.001$ A vs B; [c] $p < 0.001$ A vs E; [d] $p < 0.001$ A vs D; NS: D vs E	[e] $p = 0.002$ A vs C; [f] $p < 0.001$ B vs C
Poliovirus shedding at 19 weeks: *n* (%)	12/203	5.9%	119/196	60.7%	89/156	57.1%	99/151	65.6%	122/211	57.8%	NS: C vs D	
Type 3												
Seroconversion by 14 weeks: *n* (%)	174/205	84.9%[b,c,e]	181/203	89.2%[a,f]	54/161	33.5%[e,f]	22/155	14.2%[c,d]	153/211	72.5%[a,b,d]	[a] $p < 0.001$ B vs E; [b] $p = 0.003$ A vs E; [c] $p < 0.001$ A vs D; [d] $p < 0.001$ D vs E; NS: A vs B	[e] $p < 0.001$ A vs C; [f] $p < 0.001$ B vs C
Priming response by 15 weeks: *n* (%)†	–	–	–	–	84/87	96.6%	94/107	87.9%	–	–		
Cumulative effect of one dose (seroconversion and priming): *n* (%)†	–	–	–	–	129/132	97.7%	115/128	89.8%	–	–		
Seroconversion by 18 weeks: *n* (%)	192/203	94.6%	188/200	94.0%	152/156	97.4%	135/152	88.8%	198/211	93.8%	NS: B vs E; A vs B; A vs E; A vs D; D vs E	NS: A vs C; B vs C
Poliovirus shedding at 19 weeks: *n* (%)	16/203	7.9%	12/196	6.1%[a]	50/156	32.1%	64/151	42.4%	29/211	13.7%[a]	[a] $p = 0.013$ B vs E; NS: C vs D	

NS, not significant; tOPV, trivalent oral poliovirus vaccine (OPV); bOPV, bivalent OPV; IPV, inactivated poliovirus vaccine; f-IPV, fractional IPV.

* Test comparison of IPV (Arm C) and f-IPV (Arm D) presented in Fig. 2.

** Bonferronni correction. Significance at $p < 0.0125$.

† Analysis restricted to those with serological results at 6, 14, 15 and 18 weeks.

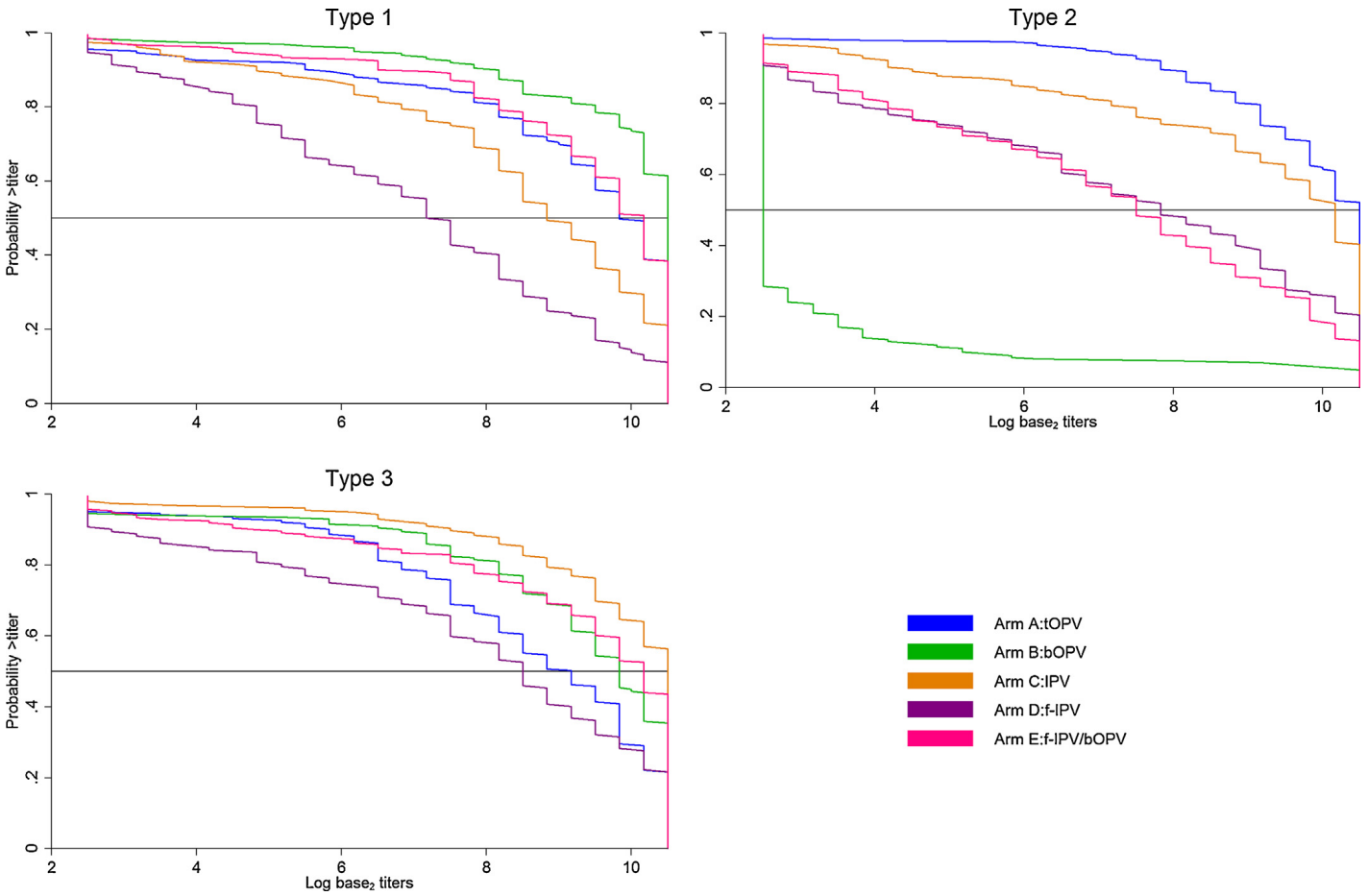

Fig. 3. Reverse cumulative antibody titers at 18 weeks of age by study arm.

as vaccination coverage in many high-risk countries is higher at age 6 weeks compared with age 14 weeks [6].

The study confirms that bOPV is more immunogenic than tOPV for poliovirus types 1 and 3 [15]; however, after 3 doses, the differences in seroconversion are small and high titers of antibodies were observed after administration of both vaccines. Prior field assessments of tOPV have reported substantially lower effectiveness though those estimates have been based on parental report of the number of vaccine doses received [20,21]. This study demonstrates a high immunogenicity of tOPV in a developing country with a tropical climate [22–24].

IPV demonstrated a higher immunogenicity compared with f-IPV for priming with one dose and seroconversion with one or two doses. These results address a prior identified information need by SAGE to collect more evidence on the comparative immunogenicity of f-IPV and IPV [8]. Also these results are consistent with other studies that have reported lower immunogenicity of a one-fifth IPV dose compared with IPV [7,14,25]. The findings of this study confirm the safety of NanoPass MJ-600 in intradermal f-IPV administration, a device that had not been previously used for f-IPV administration.

The stool excretion results demonstrate a minimal reduction in type 2 excretion with IPV and f-IPV recipients compared with bOPV recipients, who did not receive any type 2 vaccine. Also a vaccination schedule of f-IPV/bOPV reduced the percent of participants who excreted type 1 or 3 polioviruses 1 week after receiving tOPV compared to the use of IPV or f-IPV alone. Although the percent excreting poliovirus in the f-IPV/bOPV arm was significantly higher than those in the bOPV arm, the absolute difference was not large. A prior study with tOPV demonstrated the substantial reduction in excretion of polioviruses with 1–2 doses of tOPV with minimal reduction with additional doses [26]. These findings taken together with noteworthy priming associated with IPV at age 6 weeks support evaluating polio vaccination schedules with IPV only as the first poliovirus vaccine followed by OPV.

This study has notable limitations. First, transmission of OPV received by other children in the community was observed. However, the effect of community transmission was low with only 14% type 2 seroconversion over 12 weeks in the bOPV arm [23,27]. Second, in the assessment of priming, the primary as well as secondary (challenge at 14 weeks) vaccines had different routes of administration and dosage between IPV and f-IPV arms, which limits comparison. Lastly, assessment of MJ600 performance was limited to safety and injection quality associated with the device and we could not compare immunogenicity of IPV administered by MJ600 with standard needle and syringe for intradermal administration.

Overall, findings from this study address several previously identified information gaps with regard to primary routine polio vaccine performance and could help simplify and expand polio vaccination policy options. The study supports the safety and comparable immunogenicity of tOPV and bOPV for types 1 and 3 poliovirus and demonstrates the lack of non-inferiority of one-fifth f-IPV to IPV. Most importantly, the study shows the promising degree of priming with an early (6 week) dose of IPV. A useful next step would be to compare priming at age 6 weeks to that with the SAGE-recommended IPV schedule at age $\geq$14 weeks.

Funding

This study was funded by the Centers for Disease Control and Prevention.

Contributors

AA prepared the first draft of the manuscript and all authors reviewed and approved the manuscript. AA, CFE, HG, MAP, SW, MSO and WW contributed to the design of the study. The design team jointly developed the trial implementation strategy with KZ, SPL, JDH, MY and TBI.

WW and MSO contributed to laboratory testing. AA and HG contributed to data analysis. All authors contributed to interpretation of study results.

Conflict of interest

All authors declare that they have no conflict of interest.

Acknowledgments

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention. We thank the study staff at Mirpur site in Dhaka, Bangladesh; Claire Capshew, Deborah Moore, Yiting Zhang, Sharla McDonald, Larin McDuffie, William Hendley, Patricia Mitchell and Mario Nicolas at the Polio and Picornavirus Laboratory Branch in Centers for Disease Control and Prevention; all parents and infants who participated in this study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.09.039.

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ORIGINAL ARTICLE

Priming after a Fractional Dose of Inactivated Poliovirus Vaccine

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ABSTRACT

BACKGROUND

To reduce the costs of maintaining a poliovirus immunization base in low-income areas, we assessed the extent of priming immune responses after the administration of inactivated poliovirus vaccine (IPV).

METHODS

We compared the immunogenicity and reactogenicity of a fractional dose of IPV (one fifth of a full dose) administered intradermally with a full dose administered intramuscularly in Cuban infants at the ages of 4 and 8 months. Blood was collected from infants at the ages of 4 months, 8 months, 8 months 7 days, and 8 months 30 days to assess single-dose seroconversion, single-dose priming of immune responses, and two-dose seroconversion. Specimens were tested with a neutralization assay.

RESULTS

A total of 320 infants underwent randomization, and 310 infants (96.9%) fulfilled the study requirements. In the group receiving the first fractional dose of IPV, seroconversion to poliovirus types 1, 2, and 3 occurred in 16.6%, 47.1%, and 14.7% of participants, respectively, as compared with 46.6%, 62.8%, and 32.0% in the group receiving the first full dose of IPV (P<0.008 for all comparisons). A priming immune response to poliovirus types 1, 2, and 3 occurred in 90.8%, 94.0%, and 89.6% of participants, respectively, in the group receiving the fractional dose as compared with 97.6%, 98.3%, and 98.1% in the group receiving the full dose (P=0.01 for the comparison with type 3). After the administration of the second dose of IPV in the group receiving fractional doses, cumulative two-dose seroconversion to poliovirus types 1, 2, and 3 occurred in 93.6%, 98.1%, and 93.0% of participants, respectively, as compared with 100.0%, 100.0%, and 99.4% in the group receiving the full dose (P<0.006 for the comparisons of types 1 and 3). The group receiving intradermal injections had the greatest number of adverse events, most of which were minor in intensity and none of which had serious consequences.

CONCLUSIONS

This evaluation shows that vaccinating infants with a single fractional dose of IPV can induce priming and seroconversion in more than 90% of immunized infants. (Funded by the World Health Organization and the Pan American Health Organization; Australian New Zealand Clinical Trials Registry number, ACTRN12610001046099.)

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N Engl J Med 2013;368:416-24.
DOI: 10.1056/NEJMoa1202541

In 1988, the World Health Assembly resolved to eradicate poliomyelitis globally by the year 2000.[1] Although substantial progress toward the eradication goal has been achieved, by the end of 2010,[2] poliovirus types 1 and 3 continued to circulate in four countries in which poliomyelitis is endemic, and periodic importations led to epidemic spread in more than 20 countries in 2009 and 2010.[3-5] Concurrently, progress in India suggested that interruption of transmission might be feasible in 2011,[6] and indeed, no cases of infection with wild-type poliovirus have been reported in India since January 13, 2011.[7]

In tandem with these eradication efforts, the planning for the posteradication era began more than a decade ago. The most important goal — to cease use of the oral poliovirus vaccine (OPV) after the eradication of wild-type poliovirus — was suggested in 1997[8] and formally endorsed by technical oversight committees in 2004[9] and 2008.[10] The prerequisites for OPV cessation have been reported,[11] the vaccination options have been identified,[12] and the risks of paralytic disease from poliomyelitis after cessation of the OPV have been broadly defined.[13]

In 2008, the World Health Assembly asked the World Health Organization (WHO) to "develop appropriate strategies and products for managing risks, including safer processes for IPV [inactivated poliovirus vaccine] production and affordable strategies for its use."[14] A number of strategies intended to make IPV affordable in developing countries are being evaluated, including schedule reduction (administration of fewer doses), dose reduction (the use of fractional-dose IPV), antigen reduction (with the use of traditional and novel adjuvants), optimization of production processes (increases in cell density, use of new cell lines, and use of alternative inactivation agents), and production of Sabin–IPV in developing countries.[15-17] The schedule-reduction approach, in which two doses of IPV are administered, has been evaluated in multiple studies,[18] which suggest that two doses of IPV could induce seroconversion to all three poliovirus serotypes in more than 90% of those vaccinated, provided that an appropriate schedule is followed (i.e., the first dose is not administered before 2 months of age, and the interval between the doses is 2 months or more).

Given that the immunogenicity of IPV is greatly affected by maternally derived antibodies,[19,20] we conducted a two-dose trial of fractional as compared with full-dose IPV administered in infants at the ages of 4 and 8 months.[21,22] Given the interest in further reducing the costs of IPV use, we also evaluated immune responses after one dose. We chose Cuba as the trial site because oral poliovirus vaccine (OPV) is used only twice a year in national campaigns (usually February and April) in Cuba, thereby minimizing the exposure of the study population to the Sabin virus.[23]

Methods

Study Design

We conducted a randomized, controlled clinical trial in which laboratory investigators were unaware of group assignments. Investigators at study sites were aware of group assignments, since different methods were used to administer each vaccine type (intradermal injection for the fractional dose and intramuscular injection for the full dose). The field work was conducted between July 6, 2009, and January 28, 2009, at 13 vaccination sites in 4 districts of Camagüey Province, Cuba. We had three specific objectives: first, to compare humoral antibody responses (seroconversion and antibody titer) after administration of two fractional doses of IPV or two full doses of IPV, the first at 4 months of age and the second at 8 months of age; second, to evaluate the dose-specific immune responses, including one-dose priming immune responses; and third, to determine what adverse events would follow the fractional-dose vaccination as compared with the full-dose vaccination. (For full details of the study design, see the protocol, available with the full text of this article at NEJM.org.)

Study Population

Recruitment took place during the routine immunization visit at 2 months of age, at which time the parent or legal guardian was informed about the study and invited to participate. Participation was contingent on provision of informed consent by the parent or guardian, an Apgar score of 9 or more at 5 minutes (according to a review of records), a birth weight of 2.5 kg or more (according to records), a medical examination suggesting that the infant was healthy and breast-fed, and a weight for height above the 10th percentile on a growth chart at the age of 4 months. If an infant's weight for height fell below the 10th per-

centile on the growth curve during the study period, the infant was withdrawn from the study.

STUDY OVERSIGHT

The study was approved by the Cuban National Regulatory Agency and Ministry of Health; the institutional review board of the Pedro Kouri Institute, in Havana, Cuba; the ethical review committees of the Camagüey Provincial Health Office, in Cuba; and the WHO, in Geneva. The study was carried out in compliance with Good Clinical Practice guidelines. All the authors vouch for the completeness and accuracy of the data and analyses presented and for the fidelity of the study report to the protocol. All study vaccines were donated by Netherlands Vaccine Institute (NVI). NVI had no role in the study design or implementation, data analysis, or manuscript preparation or the decision to submit the manuscript for publication.

STUDY PROCEDURES

Infants born during either March or April 2009 in the participating health center catchment areas were eligible for participation. These infants were randomly assigned to receive either a fractional dose of IPV (0.1 ml, or one fifth of the full dose) or a full dose at the ages of 4 and 8 months. Randomization was performed by having parents draw sealed envelopes containing the group assignment just before administration of the first vaccine dose and after a pediatrician's evaluation to determine whether the infant met the inclusion criteria.

The vaccines (produced by NVI) were formulated to contain at least 32-D, 8-D, or 40-D antigen units of poliovirus serotypes 1, 2, and 3, respectively, and were shipped in appropriate cold-chain conditions from the manufacturer to Havana. They were administered intradermally with a needle-free device (Biojector 2000, Bioject Medical Technologies) or intramuscularly with an "auto-disable" syringe and needle. The needle-free device was approved by the U.S. Food and Drug Administration for intramuscular and subcutaneous administration and on a case-by-case base for investigational intradermal administration with the use of a spacer. The device has been used previously to administer fractional-dose IPV[22,23] and was approved by the Cuban Medical Device Agency for use in this study.

After each vaccination, the infants were monitored for 60 minutes for immediate adverse events and were also evaluated by qualified medical staff during home visits at 24 and 48 hours. Adverse events were classified as minor, moderate, or severe in intensity and as serious or not serious in consequence. No other vaccines were administered concurrently with or for an interval of 2 weeks before or after each IPV vaccination.

Blood specimens were collected at 4 months (baseline), at 8 months, at 8 months 7 days, and at 8 months 30 days. An automated, single-use, heelstick device (Tenderfoot, International Technidyne) was used to collect the specimens. After coagulation, the serum was separated, frozen, and stored at the study site at −20°C until transport to the Pedro Kouri Institute. The specimens were tested in triplicate with a modified neutralization assay for antibodies to poliovirus types 1, 2, and 3.[24,25] The starting dilution was a reciprocal titer of 8. Seropositivity (a detectable antibody level) was defined as a reciprocal titer of 8 or more.[26] Seroconversion was defined as an increase in the antibody titer that was four times as high as the baseline titer. Participants who did not meet this criterion for seroconversion were also evaluated for seroconversion on the basis of an increase in the antibody titer that was at least four times as high as the expected value of the decline in maternally derived antibodies. The half-life of antibody decay was assumed to be 30 days.[20] For infants whose blood was seronegative, a change to seropositive status in a successive specimen (i.e., a reciprocal titer of 8 or more) was considered to indicate seroconversion. The definition of a priming immune response was the absence of seroconversion after the first dose of IPV and an antibody titer at 8 months 7 days that was four times as high as the titer at 8 months, or a nondetectable reciprocal titer at 8 months and a detectable reciprocal titer at 8 months 7 days.[27]

STATISTICAL ANALYSIS

We calculated that a minimum of 138 participants in each of the two study groups would be needed to detect a difference of 20% or more, at an alpha level of 0.05 and a beta level of 0.10 (two-tailed test). For those calculations, we assumed seroconversion end points of 40% and 60% for the fractional-dose and full-dose groups, respectively. To account for attrition, we increased the sample size to 160 per group.

Statistical analyses were performed with the

use of statistical packages from the R Foundation for Statistical Computing[28] and the SAS Institute (version 6.4).[29] Comparisons of the proportions of infants with seroconversion in the study groups were conducted with the use of chi-square tests (with the Yates-corrected test, or with Fisher's exact test if the number of data in a cell was 5 or less). The differences in the distribution of antibody titers were tested with the Kolmogorov–Smirnov nonparametric method.[30] The 95% confidence intervals for median values were derived by means of simulation.[31] A single post hoc subgroup analysis was conducted.

RESULTS

STUDY POPULATION

A total of 320 participants underwent randomization, and 310 participants (96.9%) completed the study (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Among the 10 participants who did not complete the study, 3 were in the fractional-dose group and 7 were in the full-dose group. The reasons for withdrawal or exclusion were as follows: 3 participants moved out of the study area, 1 had a respiratory illness, and 6 had evidence of exposure to OPV through contact with close relatives who had been vaccinated during the February and March 2009 campaigns.

After randomization, the baseline attributes, type-specific seroprevalence, and poliovirus antibody titers of the two study groups were similar except with regard to the seroprevalence comparison for poliovirus type 2 (P=0.002). Poliovirus seroprevalence in the fractional-dose and full-dose groups was 29.3% and 33.3% for type 1, 34.4 and 46.4% for type 2, and 8.3% and 9.2% for type 3, respectively (Table 1).

Table 1. Baseline Characteristics of the Study Participants.*

Variable	Fractional Dose of IPV (N=157)	Full Dose of IPV (N=153)
Male sex — no. (%)	82 (52.2)	87 (56.9)
Median birth weight (95% CI) — kg	3.40 (3.35 to 3.50)	3.42 (3.40 to 3.54)
Poliovirus type 1		
Seroprevalence — no. (%)	46 (29.3)	51 (33.3)
Median reciprocal titer (95% CI)†	<8 (<8 to <8)	<8 (<8 to <8)
Poliovirus type 2		
Seroprevalence — no. (%)	54 (34.4)	71 (46.4)
Median reciprocal titer (95% CI)†	<8 (<8 to <8)	<8 (<8 to <8)
Poliovirus type 3		
Seroprevalence — no. (%)	13 (8.3)	14 (9.2)
Median reciprocal titer (95% CI)†	<8 (<8 to <8)	<8 (<8 to 8)

* None of the between-group differences were significant except for the comparison of poliovirus type 2 seroprevalence (P=0.002 by a Yates-corrected chi-square test). Seroprevalence was defined as an antibody titer of at least 1:8. IPV denotes inactivated poliovirus vaccine.

† The median titer and corresponding 95% confidence interval (CI) are below or above observed dilution ranges (i.e., reciprocal titer, 8 to 1224).

CHANGES IN IMMUNITY

After a single dose of IPV, seroconversion to poliovirus types 1, 2, and 3 occurred in 16.6%, 47.1%, and 14.7% of infants in the fractional-dose group and in 46.6%, 62.8%, and 32.0% of infants in the full-dose group, respectively (P<0.008 for all comparisons). The definition of a priming immune response to poliovirus types 1, 2, and 3 was met in 90.8%, 94.0%, and 89.6% of infants in the fractional-dose group and 97.6%, 98.3%, and 98.1% of those in the full-dose group, respectively; only the between-group comparison for poliovirus type 3 was significant (P=0.01). The cumulative rates of seroconversion to poliovirus types 1, 2, and 3 after two doses of IPV were 93.6%, 98.1%, and 93.0% in the fractional-dose group and 100%, 100%, and 99.4% in the full-dose group, respectively (P<0.006 for the between-group comparisons of types 1 and 3); the between-group differences in the rates of cumulative seroconversion after two doses for the various vaccines were as follows: 6.4 percentage points for type 1 (95% confidence interval [CI], 2.0 to 11.7), 1.9 percentage points for type 2 (95% CI, –1.5 to 5.9), and 6.4 percentage points for type 3 (95% CI, 1.6 to 11.9) (Table 2).

The median reciprocal antibody titers against poliovirus type 1 in the two groups were similar at 4 months (<8) and remained lower than 8 or increased marginally (to 11) at 8 months. However, at 8 months 7 days, the titers in both groups showed a robust increase (to 713 in the fractional-dose group and to 1448 or higher in the full-dose group, P<0.001); the titers remained relatively stable at 8 months 30 days (450 in the fractional-dose group and 1448 or higher in the full-dose group, P<0.001). Similarly, the median reciprocal antibody titers against poliovirus type 2 were similar at 4 months (<8), increased at 8 months to 9 in the fractional-dose group

Table 2. Rates of Seroconversion and Priming Immune Response after One or Two Doses of Inactivated Poliovirus Vaccine for Poliovirus Types 1, 2, and 3.*

Immune Response	Fractional IPV Dose (N=157)	Full IPV Dose (N=153)	P Value	Between-Group Difference (95% CI)
	no./total no. (%)			*percentage points*
Poliovirus type 1				
Seroconversion after first dose	26/157 (16.6)	71/153 (46.4)	<0.001	29.8 (19.2 to 39.6)
Priming response	119/131 (90.8)	80/82 (97.6)	0.1	6.8 (–1.3 to 13.7)
Seroconversion between visits 3 and 4	2/12 (16.7)	2/2 (100)	0.13	83.3 (–3.2 to 97.1)
Seroconversion after second dose	121/131 (92.4)	82/82 (100)	0.01	7.6 (0.9 to 14.0)
Cumulative seroconversion	147/157 (93.6)	153/153 (100)	0.002	6.4 (2.0 to 11.7)
Poliovirus type 2				
Seroconversion after first dose	74/157 (47.1)	96/153 (62.7)	0.008	15.7 (4.1 to 26.6)
Priming response	78/83 (94.0)	56/57 (98.2)	0.42	4.3 (–5.4 to 12.5)
Seroconversion between visits 3 and 4	2/5 (40.0)	1/1 (100)	>0.99	60.0 (NP)
Seroconversion after second dose	80/83 (96.4)	57/57 (100)	0.41	3.6 (–4.7 to 10.9)
Cumulative seroconversion	154/157 (98.1)	153/153 (100)	0.26	1.9 (–1.5 to 5.9)
Poliovirus type 3				
Seroconversion after first dose	23/157 (14.6)	49/153 (32.0)	<0.001	17.3 (7.5 to 26.9)
Priming response	120/134 (89.6)	102/104 (98.1)	0.01	8.5 (1.5 to 15.5)
Seroconversion between visits 3 and 4	3/14 (21.4)	1/2 (50.0)	0.90	28.6 (NP)
Seroconversion after second dose	123/134 (91.8)	103/104 (99.0)	0.018	7.2 (0.9 to 13.7)
Cumulative seroconversion	146/157 (93.0)	152/153 (99.3)	0.006	6.4 (1.6 to 11.9)

* Seroconversion was defined as an increase in the antibody titer that was four times as high as the expected decline in maternally derived antibodies. Cumulative seroconversion reflects the sum of the seroconversions occurring after the first and the second dose. P values were calculated with the use of chi-square tests (with the Yates-corrected test, or with Fisher's exact test if the number of participants in a cell was 5 or fewer). NP denotes not presented (i.e., the numbers of participants in the cells were too small to calculate meaningful 95% confidence intervals).

and 28 in the full-dose group, rose at 8 months 7 days to 1448 or higher in both groups (P<0.001), and at 8 months 30 days remained at 898 in the fractional-dose group and 1448 or higher in the full-dose group (P<0.001). Finally, the median reciprocal antibody titers to poliovirus type 3 at 4 months and 8 months were lower than 8 in both groups, increased at 8 months 7 days to 357 in the fractional-dose group and to 1448 or more in the full-dose group (P<0.001), and then decreased at 8 months 30 days to 71 in the fractional-dose group and 898 in the full-dose group (P<0.001) (Table 3).

Figure 1 shows median reciprocal antibody titers according to study group and seroconversion status after the first dose of IPV at 4 months. As expected, the median titers differed significantly between the groups at 8 months; they did not differ significantly at 8 months 7 days or at 8 months 30 days (with the exception of the titer for poliovirus type 2 in the fractional-dose group and for poliovirus type 3 in the full-dose group).

ADVERSE EVENTS

Most adverse events were classified as minor in intensity and not serious in consequence (Table 4). Minor reactions at the injection site were frequent, especially induration, pain, and redness. There were 114 adverse events in the fractional-dose group, as compared with 11 in the full-dose group. Among the 114 adverse events in the fractional-dose group, 84 (73.7%) were redness at the injection site, 25 (21.9%) induration at the injection site, 3 (2.6%) a temperature of 38.5°C or higher, and 2 other events. All injection-site reactions but one involved an area smaller than 5 mm in diameter. As expected, the prevalence of these events in the fractional-dose group, which received in-

tradermal injections, was significantly higher than that in the full-dose group, which received intramuscular injections (Table 4).

DISCUSSION

This study provides data on a priming immune response after the administration of an initial fractional dose of IPV and on seroconversion after the administration of a first dose, second dose, or cumulative two-dose schedule of IPV (4 and 8 months after birth) that may be appropriate after wild-type poliovirus has been eradicated. First, the study showed that after a first dose of IPV, seroconversion and priming resulted in an immune response in at least 90% of infants. Second, it showed that the administration of IPV in infants at 4 months and 8 months of age resulted in seroconversion in more than 90% of infants, with correspondingly high antibody titers, regardless of whether fractional or full doses were used. Third, the study showed that although the median antibody titer in both study groups was high, it was significantly lower in the fractional-dose group at both 7 days and 30 days after a second IPV vaccination. No serious safety problems were identified.

The primary goal of the study was to assess the priming immune response after a single dose of IPV. Our results suggest that 86.9% or more of infants who did not undergo seroconversion after a first dose of IPV did have a priming immune response. The magnitude of the increase in median antibody titers in the 7-day period after administration of a second dose of IPV is noteworthy, as is the decline in titers between the assessments performed at 8 months 7 days and 8 months 30 days. We are not suggesting that a priming immune response is protective against clinical disease, but we believe that this may prove to be the case when more data are available.

Data from one efficacy trial[32] suggest that the efficacy of a single dose of IPV is low, but the trial had limitations. The confidence intervals for the efficacy estimates were wide.[32] On the other hand, data from countries in which a single dose of IPV was followed by a dose of OPV, such as Hungary, and analyses from other countries in which a sequential schedule was used, suggest that a single dose of IPV has been efficacious against vaccine-associated paralytic poliomyelitis induced by Sabin polioviruses.[33,34]

Table 3. Median Reciprocal Antibody Titers.*

Visit	Fractional Dose of IVP (N=157)	Full Dose of IVP (N=153)	P Value†
	titer (95% CI)		
Poliovirus type 1			
4 mo	<8 (<8 to <8)	<8 (<8 to <8)	NS
8 mo	<8 (<8 to <8)	11 (9 to 14)	NS
8 mo 7 days	713 (566 to 898)‡	≥1448 (≥1448 to ≥1448)§	<0.001
8 mo 30 days	450 (357 to 566)‡	≥1448 (≥1448 to ≥1448)§	<0.001
Poliovirus type 2			
4 mo	<8 (<8 to <8)	<8 (<8 to 9)	NS
8 mo	9 (<8 to 11)	28 (18 to 36)	NS
8 mo 7 days	≥1448 (≥1448 to ≥1448)¶	≥1448 (≥1448 to ≥1448)‖	<0.001
8 mo 30 days	898 (713 to ≥1448)¶	≥1448 (≥1448 to ≥1448)‖	<0.001
Poliovirus type 3			
4 mo	<8 (<8 to <8)	<8 (<8 to <8)	NS
8 mo	<8 (<8 to <8)	<8 (<8 to <8)	NS
8 mo 7 days	357 (225 to 566)**	≥1448 (≥1448 to ≥1448)††	<0.001
8 mo 30 days	71 (36 to 113)**	898 (566 to ≥1448)††	<0.001

* Median titers and corresponding 95% confidence intervals are below or above observed dilution ranges (i.e., reciprocal titer, 8 to 1224).
† P values were calculated in accordance with Kolmogorov–Smirnov nonparametric testing of antibody titer distribution. NS denotes not significant.
‡ P=0.001 for the within-group comparison.
§ P=0.02 for the within-group comparison.
¶ P=0.004 for the within-group comparison.
‖ P=0.30 for the within-group comparison.
** P<0.001 for the within-group comparison.
†† P=0.001 for the within-group comparison.

These data are particularly relevant to the current policy discussions regarding an eventual global switch from trivalent OPV to bivalent OPV for both routine and supplementary immunization. We found that for poliovirus type 2, a single fractional dose produced seroconversion in almost half the infants (47.1%) and a priming response in almost all of those who did not undergo seroconversion (94.0%). Furthermore, two-dose schedules have been shown to yield seroconversion rates of more than 80% in studies in Cuba and other countries, particularly when the doses are administered at 2 and 4 months of age.[18,21,22] Our results extend these findings and suggest that for the post-eradication era, two doses of IPV given at the ages of 4 and 8 months (which in our study resulted in almost 100% seroconversion and high antibody titers in the full-dose group, with moderately lower seroconversion rates and significantly lower antibody ti-

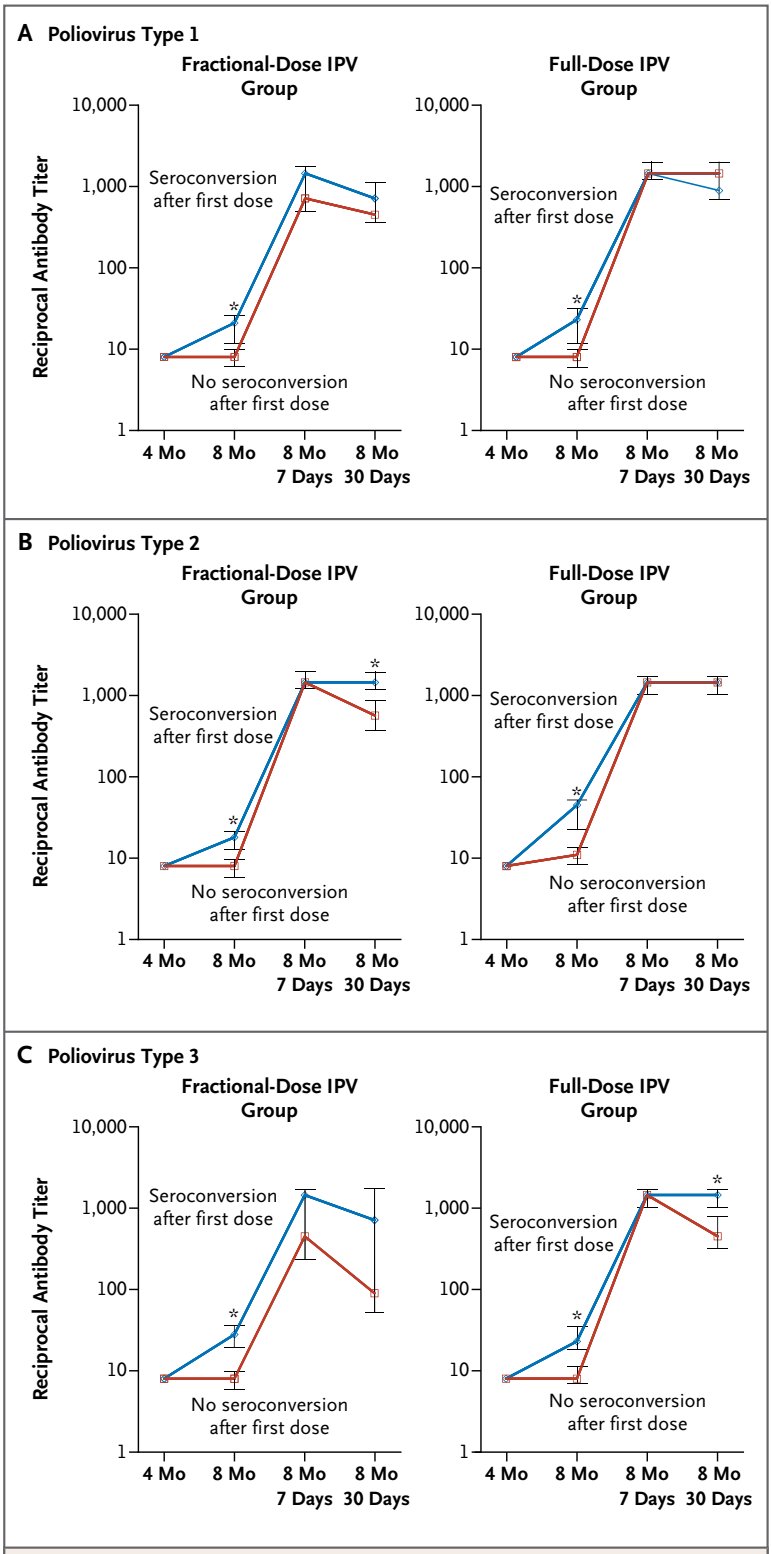

Figure 1. Median Antibody Titers at Each Study Visit According to Study Group and Conversion Status after First Dose.

Median antibody titers are shown for type 1 poliovirus in Panel A, for type 2 poliovirus in Panel B, and for type 3 poliovirus in Panel C. I bars denote 95% confidence intervals, and asterisks a significant difference at P<0.05.

ters in the fractional-dose group) could provide a lower-cost alternative to the three-dose and four-dose schedules used currently.

This trial also expands the number of policy options that could make IPV affordable for use in developing countries. First, two fractional doses of IPV administered on an appropriate schedule (e.g., an older age at administration and a longer interval between doses) appear to induce seroconversion in a high proportion of vaccinees (>90%) and would immediately reduce the cost of vaccination on such a schedule from the current $6.00 per vaccinee (based on UNICEF's IPV procurement price of approximately $3.00 per dose) to $1.20. Second, a one-dose IPV priming schedule could further reduce the cost to 60 cents. Since the other strategies for making IPV affordable are expected to further reduce its price, the WHO expects the tiered pricing of IPV for developing countries to be decreased to the break-even price with OPV, at less than 50 cents per immunizing dose.[35-37]

The study has some limitations. Although every effort was made to prevent secondary exposure to the vaccine virus, we identified and withdrew six infants because of demonstrated or probable exposure to OPV administered during the February and May 2009 immunization campaigns in Cuba. One remaining issue may be uncertainty regarding the long-term persistence of antibody titers in developing countries. Data from industrialized countries suggest that antibody titers decline rapidly after immunization and then remain relatively stable for many years.[38]

There were more minor adverse events associated with the use of fractional-dose IPV than with full-dose IPV owing to the fact that the fractional doses were administered intradermally. Previous surveys of parents have shown that the increase in minor local adverse events after intradermal administration of IPV did not affect their preference with respect to the route of administration.[21,22]

Our study shows that the administration of a single fractional dose of IPV for priming is a feasible, lower-cost alternative to schedules in which multiple full doses are used. It is also a feasible alternative to hexavalent combination IPV vaccines when available for use in developing countries. A fractional dose could be administered together with the diphtheria–tetanus toxoids and pertussis vaccine (DTP) in infants between 4 and

Table 4. Adverse Events.*

Event	Fractional Dose of IVP (N=157)		Full Dose of IVP (N=153)	
	Dose 1	Dose 2	Dose 1	Dose 2
	number (percent)			
Temperature ≥38.0°C	1 (0.6)	2 (1.3)	2 (1.3)	0
Infiltration†	0	1 (0.6)	0	0
Redness	47 (30.0)‡	37 (23.6)§	3 (2.0)‡	2 (1.3)§
Induration	11 (7.0)¶	14 (8.9)‖	2 (1.3)¶	1 (0.7)‖
Other	1 (0.6)**	0	1 (0.7)††	0

* Among the five infants with elevated temperatures, the temperatures were between 38.0 and 38.9°C, and the elevated temperature was classified as moderate in intensity; all other adverse events were classified as minor, except in the case of one infant in the fractional dose group who after the first dose had an induration measuring 0.6 mm in diameter, which was classified as moderate in intensity.
† Infiltration was defined as a combination of local signs and symptoms (redness, induration, pain).
‡ P<0.001 for the between-group difference in redness after dose 1.
§ P<0.001 for the between-group difference in redness after dose 2.
¶ P=0.03 for the between-group difference in induration after dose 1.
‖ P=0.002 for the between-group difference in induration after dose 2.
** This patient had restlessness.
†† This patient had weakness.

6 months of age, or together with measles vaccine in infants between 9 and 12 months of age. If full protection against poliomyelitis is needed (e.g., if an outbreak is anticipated), a second fractional dose or a full dose could be administered rapidly in mass campaigns. This second dose would be expected to rapidly boost antibody titers to high levels (especially in those whose immune system has been primed). In addition, since vaccine efficacy is probably dependent on antibody production, this boost would protect individual children from the paralytic consequences of poliomyelitis at an affordable cost.

Supported by the World Health Organization (WHO), the Pan American Health Organization (PAHO), and the Netherlands Vaccine Institute, which donated the study vaccines.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the study staff at the field sites in Camagüey and at the Pedro Kouri Institute (IPK), especially Damarys Concepción (IPK Epidemiology Branch); Nadezhda Gonzalez, Niurka Pereda, Luis Morier, Dianeya Mendoza, Guadalupe Guzmán, and Alina Llop (IPK Microbiology Branch); and Manuel Silva, Jorge de Armas, Deysi Torres, and the family doctors and nurses at the clinics included in the study (Camagüey); the staff at the PAHO–WHO Havana office, especially Jorge Hadad, and at the Cuban Ministry of Health for help with facilitating the trial; the external monitor of the study, Ricardo Palacios, who contributed significantly to the success of the trial; and the parents and infants who participated in the trial.

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Concept Note

Implementation in the Context of Health Systems Strengthening (HSS) and Universal Health Coverage (UHC)

Session 6

Meeting of Strategic Advisory Group of Experts (SAGE) on Immunization

12-14 April 2016

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Implementation in the Context of Health Systems Strengthening and Universal Health Coverage

Introduction

This concept note will further elaborate some of the critical issues related to implementation of immunization services within the broader context of health systems strengthening (HSS) and universal health coverage (UHC) that will be presented during the session 6, Implementation in the Context of HSS and UHC during the SAGE meeting, 12-14 April 2016.

This session has been requested because over the past few years the world has seen a decline and/or stagnation in the immunization coverage. The approaches, structures and method of delivery of services used to actually deliver these life-saving innovations are largely those that were developed in the 1970's and are not optimized for modern and contemporary vaccine programs and health system. The result is that the field lacks a mature depth of scientific evidence, rigorous data, set of methods to inform the optimization of vaccine implementation within the complex health system. A central characteristic of this science is the systems nature of the problems we seek to solve. While there is reasonable know how on what the various core components of an immunization system are and how they should function in a silo, there is a substantial missing understanding on how the interaction of all the components can be effectively integrated to make the holistic system work well as a whole. At present there is a focus on single component solutions separately, rather than the more challenging thinking required for systems approaches.

This session will therefore, inform the SAGE and discuss how to sustain the provision of immunization services as part of integrated health services delivery to achieve universal health coverage. The session will provide an overview of the health systems, including the complexity of implementation and options for achieving greater equity and quality in health care. It will build from experiences related to implementation of select critical components of the health systems, such as supply chains, planning and micro-planning and financial efficiency and gains. Based on experience from ebola, it will highlight the importance of resilience and application of lessons learnt. SAGE will be asked to provide feedback, including on operations research agenda including on a systems based approach for improving immunization coverage and closing equity gaps.

The adoption of the Millennium Declaration in 2000 by all member states of the UN was a defining moment for the international community. The Declaration, the culmination of a series of international conferences and summits beginning in 1990 with the World Summit for Children, embodied a synthesis of the goals set by these international development conferences and a body of international norms and laws that had been codified over the previous half-century. The original 18 Millennium Development Goals (MDG) targets were lifted verbatim from the Millennium Declaration and therefore represented the consensus of member states over a wide range of development areas.

As reflected in the MDGs, the Declaration also represented a new approach to development, with a full recognition that development is not exclusively economic, but also embraces human social and environmental dimensions. The MDGs also reflect a shift in emphasis from inputs to results. It also set specific measurable and time-bound targets for each Goal, with progress to be measured on the basis of a list of internationally-agreed indicators.

More than 15 years later, the Millennium Declaration and the MDG framework for accountability that derived from it have inspired development efforts and helped set priorities and focus interventions. In the intervening years, global initiatives and partnerships have tracked the encouraging progress made towards reducing mortality among children under-five in many countries [2].

However, this progress and the policy adjustments made to redirect trajectories towards meeting the MDG 4 on child mortality have largely occurred at national levels. Lamentably, many of the countries that have made good progress in reducing their under-five mortality rates at a national level have also experienced worsening inequities between their wealthy and poor sub-populations, as well as widening disparities across other socio-cultural group attributes such as ethnicity, geography, food security, and citizenship [3, 4].

As we move into the era of the sustainable development goals (SDGs), foundational to reducing inequities will be ensuring more effective and efficient service delivery strategies. As highlighted above under the MDGs, it is evident that to ensure an increase in immunization coverage and to maintain its sustainability, a broader approach of overall health services through an “integrated and patient centered service delivery” should be considered, particularly now as we move forward towards SDGs to achieve UHC.

We hope this paper stimulates debate on how to operationalize sustainable universal coverage for immunization as a component of strengthening integrated service delivery and serve as a call for increased collaboration to guide evidence-based strategies at sub-national levels.

Delivery Science

There is a growing community of vaccine delivery science, and a body of scientific literature around how to improve core components of the immunization system. A central characteristic of this implementation science is the systems nature of the problems which needs to be further understood to seek effective and efficient solution that would benefit the health system, provides and population. While we know what the various core components of an immunization system are and how they should function in a silo, we don't really understand how the interaction of all the components can be effectively integrated within the larger service delivery area within the health system and how to make it work well in its entirity. To operate in an efficient manner within a health system it requires health professionals views systems and their sub-components as intimately interrelated and connected to each other, believing that mastering our understanding of how things work lies in interpreting interrelationships and interactions within and between systems a "system thinking approach".

The delivery science includes research and training to understand and improve service delivery. Health-related implementation research uses the science to study practices in routine clinical care and public health systems in order to improve the quality and equity of health care. It also includes the study of factors that influence health care professionals and organizations and the factors influencing users of health care services, thus covering demand and supply. Implementation research often involves impact research, which includes research aimed at understanding what happens during the process of implementing a change in policy, programme, or practice, that are designed to compare different approaches to implementing a change.

Knowledge about the delivery of health care to the poor is highly fragmented and focused around narrow topics reflecting funding streams. The design of programmes in the field is often ad hoc and fewer mechanisms in place to capture what practitioners learn in the field on the impact of models of delivery and effective care delivery in low resource settings. This is evident in various countries, particularly fragile states, that goes through acute or chronic crises/complex emergencies, such as South Sudan, Lybia, Syria and Afghanistan to name the few as well as the recent Ebola epidemic that affected three countries with already weak health system.

For vaccine and immunization, the Global Vaccine Action Plan (GVAP) highlights the importance of improving delivery of immunization services to achieve its goals. More specifically, the GVAP request members states, WHO and all others stakeholders to improve the logistics and the delivery of services to the difficult to reach population. This implies WHO and others to have better knowledge about the issues related to unvaccinated and under-vaccinated children, the application of delivery science is therefore crucial elements. WHO has encouraged the operational research on delivery of vaccination, the logistic of vaccination and the demand and reluctance from individuals, families and communities. Despite the recognition, these

interventions are also often still delivered in isolation and not as a component of integrated service delivery.

Delivery science will be as well an opportunity to develop multidisciplinary approach, encompassing both quantitative and qualitative approaches that require expertise in epidemiology, statistics, anthropology, sociology, health economics, political science, policy analysis, ethics, and other disciplines. Annex One contains a recent WHO background paper on Delivery Science.

Sustainable Development Goals and Universal Health Coverage (UHC)

The sustainable development “2030 Agenda” was adopted on 25 September 2015, and is composed of 17 Sustainable Development Goals (SDGs) and 169 targets to succeed the Millennium Development Goals (MDGs). The new SDGs link economic, environmental and social determinants of sustainable development with a clear focus on equity, often summarised as “leaving no-one behind”. The SDGs are for the needs of poor, disadvantaged and vulnerable populations in any country.

Under Sustainable Development Goal 3, which is to “Ensure healthy lives and promote well-being for all at all ages”, rest the targets relevant to UHC:

- By 2030, reduce the global maternal mortality ratio to less than 70 per 100,000 live births.
- By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,000 live births.
- Achieve Universal Health Coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all.

Frequently, UHC is defined as the situation where "all people have equitable access to health services and do not suffer financial hardship paying for them [5]." UHC is increasingly advocated as an important objective of health policy at global, regional, national and sub-national levels. The SDGs extend the dialogue on the achieving the Universal Right to Health [6] to every community and household, with explicit and formal pledges to engage individuals, communities and civil society in developing, implementing and overseeing health policies.

In more detail, UHC seeks to ensure that:

- All people obtain the health services they need (including prevention, promotion, treatment, rehabilitation, and palliation), of sufficient quality to be effective;
- The use of these services does not expose the user to financial hardship

Health Systems Strengthening and UHC

Strengthening, reorganizing and revising:

1. *The mix of interventions* to meet changing needs based on epidemiological and demographic trends: preventative, promotive, curative

2. *The mix of service delivery platforms* used to reach various populations with all needed services: e.g. Facility based, outreach, campaigns; but also by strategies to remove access barriers, both financial and social ones.

To advance on HSS, there is also the need to overcome the persistent misalignment between the process of developing the annual operational plan of the health sector, and the process of allocating an annual budget to the sector. Delivery science can help by identifying more effective and efficient service delivery practices, which can be more convincingly presented as high “value for money” investments that can attract and sustain domestic and external financing.

Pro-equity HSS for UHC

Persisting health inequities are not only wrong in principle but also in practice as they continue to retard progress towards achieving health goals. Understanding the pathways by which the poor and most vulnerable continue to be left out is essential if we are to move equitably and in a rights-based approach towards universal health coverage (UHC).

Pro-equity programing for health takes place within on-going global discussions around the post-2015 agenda for health, which has coalesced in recent years around “Universal Health Coverage” (UHC) as the post-2015 Sustainable Development Goal for Health.[7-9] However, clarity is lacking on what UHC means in practice [10] or how it can be best unpacked to catalyse tangible and sustainable changes to use of services by those currently left behind [11]. In practice, the feasibility of UHC is not merely a technical question but also a social and political one. Engaging civil society and fostering an enabling political environment, focused on achieving equity in health access and coverage, are therefore essential for sustaining UHC. An equity-focused approach to programming places the needs of the most deprived into account *first*, ensuring their needs are given sufficient and immediate attention to narrow the equity gaps.

Pro-equity programming must be based on knowledge of the magnitude, patterns, trends, as well as causes in inequities in child development, with specific strategic shifts tailored to address local processes of deprivation from basic services [12,13]. As yet, there is no single low-cost and robust approach available for sub-national managers to simultaneously assess financial and non-financial barriers to the uptake of RMNCH services. WHO is working with other partners to develop such sub-national assessments, which will be essential for prioritising barriers and developing solutions that quickly improve the equity as well as accelerate increases in immunization coverage[14-16].

Equity analysis: looking beyond averages

The equity situation analysis should highlight how far away the country is from reaching universal coverage of quality basic services. It should help document the unequal distribution and utilisation of services as well as make the link to the costs, quality and relevance of services on offer. The analysis should provide answers to the following questions:

(a) Which groups are deprived or at risk of deprivation from quality basic services? The location and size of each deprived sub-population should be quantified and their shortfall in coverage of access and utilisation of basic services and child outcomes should be compared to the national target, to the national average, and to the best performing group. This should include a description of the magnitude and pattern of inequity in the country along with their underlying causes.

(b) Which services/interventions/opportunities are not reaching these groups? Identification of inequities related to service delivery and service utilization.

(c) What are major structural economic, financing, socio-cultural, policy and institutional barriers to the delivery and utilization of quality basic services?

An equity-based approach "seeks to understand and address the root causes of inequity so that all children, particularly those who suffer the worst deprivations in society, have access to education, health care, sanitation, clean water, protection, and other services necessary for their survival, growth, and development"[17]. The graph below shows how immunization rates vary across different sub-populations in Vietnam, with ethnicity a significant factor in predicting immunization coverage. To the far left, the national DTP3 coverage of Vietnam is placed alongside of those from Ghana, Rwanda and Bangladesh. While the urban rich enjoy coverage closer to Ghana, poor Hmong girls have virtually no uptake of immunizations.

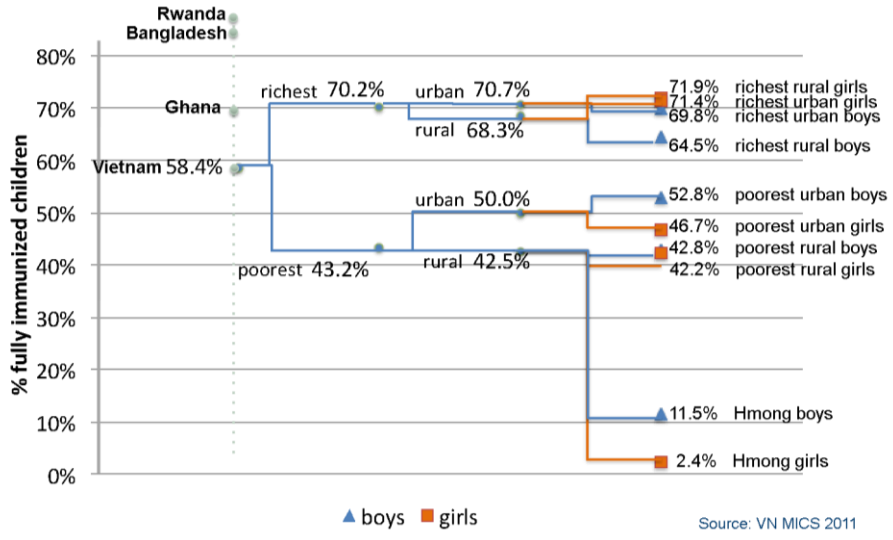


Figure 1:Immunization marginalization – Inequities within countries (Vietnam) Thiede and Koltermann [16]

While immunization, or even health managers and policy makers, may have limited ability to shape many Social Determents of Health directly, information on social and contextual factors constraining uptake of immunization service can lead to practical and effective responses. It is clear that higher levels of maternal education, for example, correlate strongly with higher immunization rates and improved child survival[16, 18]. The figure below shows that in Rwanda, mother's education is more strongly predicative of immunization coverage that wealth asset quintile.

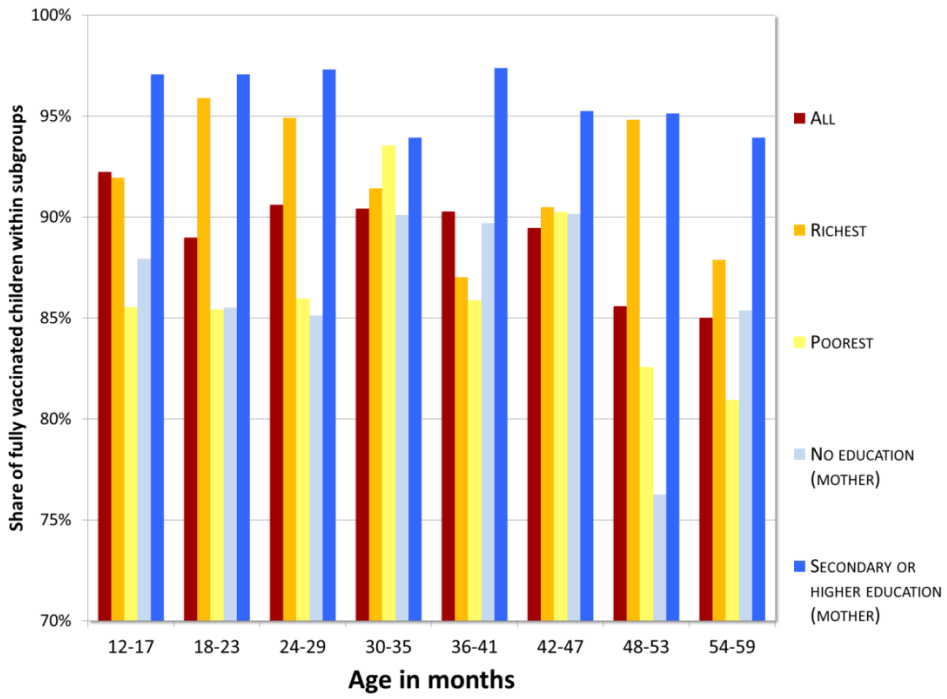


Figure 2: Full immunization by 6-month age bands, Rwanda Thiede and Koltermann [16]

A health-systems response could be taken to use information on low maternal education rates in a district to shape C4D strategies that provide targeted messages to build awareness and acceptance, among mothers with little formal schooling, of the value of immunizations [19, 20].

Pro-equity programming for immunization services

Research increasingly shows that inequities in supplying universal access to quality PHC and other essential social services have a direct and negative impact on immunization coverage, and on the equity of that coverage: "Stagnating rates of vaccination coverage may be related to increasing inequities"[19, 21]. Studies calling for urgent expansion of routine immunizations to under -and un-served communities, while acknowledging the strengths of the Reaching Every District (RED) approach [22], similarly note that Routine Immunization strengthening is only sustainable if integrated with other services [23-26]. Leveraging scarce resources to reach the last child requires new approaches robust enough to bring the full packages of services parents wish their children to use, in place of the all too common piecemeal

approach were the poor are given the crumbs off the PHC table. In Ethiopia, the evaluation of RED praises the accomplishments achieved under the integrated PHC approach used by Health Extension Workers, with immunization a core component of community-oriented services and advocacy, while in Ghana it was noted application of RED benefited integrated services including immunization [27].

Linking Immunization Coverage to Health System Strengthening

WHO, as a founding member of the GAVI Alliance, supports the work culminating in the GAVI Alliance Board declaring "the Alliance must accelerate progress on improving vaccine coverage and equity, and improve the HSS mechanism to address immunization constraints." A paper by Duclos *et.al.* notes the central role HSS plays in protecting the immunization investments and gains:

First, is the need to develop integrated strategies, whereby immunization is implemented as one of the elements of a comprehensive approach to disease control, be it meningitis, acute respiratory tract infections, pneumonia control, diarrhoeal diseases control, cancer control, antenatal care or epidemic/pandemic prevention and control. Hence, it becomes a component of integrated service delivery, which is feasible through a non traditional and system thinking approach (40). Second, the delivery of routine immunization must be seen by all as the basis and the foundation of immunization programmes and must be given attention and dedicated resources [28].

Reaching Every District to Reaching Every Community

In 2002, WHO and UNICEF, in collaboration with country governments, developed a "Reaching Every district" (RED) strategy in order to scale up immunisation coverage. The five components of the RED Strategy include supportive supervision: on-site training; community links with service delivery; monitoring and use of data for action; better planning and management of human and financial resources [22]. The advent of UHC has built upon pro-equity aspects of the Global Vaccine Action Plan (GVAP) and the Decade of Vaccines, making equity in immunisation coverage an increasing concern of global, regional and national health policy makers and planners.

Numerous studies repeat the findings in Rwanda that "the immunisation programme is not just about vaccination, it also acts as a gateway to other health services"[29]. The experience of Mongolia with the Reaching Every District (RED) strategy showed that immunization was a springboard for improving access by the poor to other PHC services, since RED was expanded to include other MCH interventions beyond vaccinations [30, 31]. This gives immunization services the potential to be a path setter for an equity approach to strengthening access to PHC services [32]. Recent work shows it would be possible to avert deaths of "147 million children, 32 million stillbirths, and 5 million women by 2035" through a comprehensive approach that targeted PHC interventions including immunization, but which also critically invested in increased family planning and ensuring adequate numbers of appropriately trained, motivated and retained staff [33].

Several practical options are being pursued across Low and Middle Income Countries (LMICs). One example is linking introduction of vaccines for pneumonia and diarrhoea to expansion of integrated Community Case Management (iCCM) to effectively treat childhood pneumonia and diarrhoea in populations currently not accessing PHC services. Equally, an integrated strategy also calls attention to the critical role of measles and pertussis vaccines in reducing pneumonia-related illness and death in children, emphasizing the role of routine immunization services to protect broader investments in child health. This is at the strategic thrust of The Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD).

The GAPPD advocates integrated activities that optimize synergies across various system strengthening efforts and ensures efficient use of primary health resources to greatly reduce under-five mortality through well-coordinated efforts to control pneumonia and diarrhea in children less than five years of age. The GAPPD notes the need to:

- *protect* children by establishing and promoting good health practices;
- *prevent* children from becoming ill from pneumonia and diarrhea by ensuring universal coverage of immunization, HIV prevention and healthy environments;
- *treat* children who are ill from pneumonia and diarrhea with appropriate treatment [1]

Addressing demand-side barriers as a means to promoting equity

Inequities in immunization are often tied to demand-side barriers that mediate the effectiveness and impact of delivery strategies. Therefore, Delivery Science research should also identify interventions that address these barriers – such as social protection and communication for development – are key to equity-based approaches.

An example is promotion of integrated social protection systems that take a multi-sector approach to address the numerous vulnerabilities faced by children and their families [34]. This also recognizes the importance of investing in demand-side interventions alongside improved service provision, and of coordinating demand and supply-side mechanisms [35]. Of course, these do not function in isolation form other cross cutting and multi-sectoral approaches that address broader Social Determinants of Health (SDH) issues, and which link Ministries of Finance, Labor, Planning, Social Policy, and Foreign Affairs, all of which are vital for resolving the contextual factors that generate inequities. While these are largely outside the scope of this paper, there are a few critical aspects of social protection that directly impact on equity in the use of immunization service.

One example of a cross-cutting initiative of recognised importance to achievement of immunization goals is improving vital registration systems [36]. Numerous studies show that children who are not birth registered are less likely to receive PHC,

Nutrition, Education, and other essential social services, and thus suffer worse health and social outcomes over their lifespan. Inequities in access and use of social services for the child leads to inequitable outcomes for the adult [37, 38].

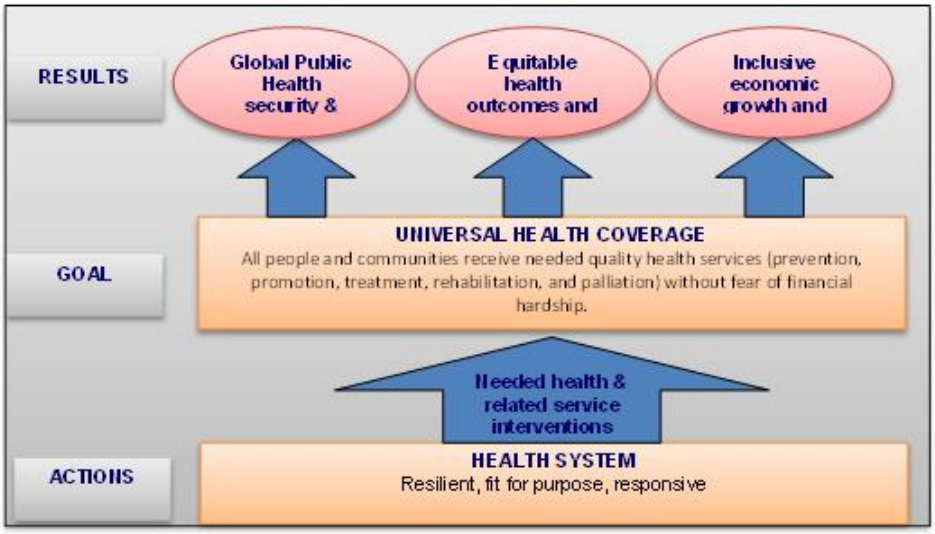
Examples relevant to joint programming efforts include attempts to strengthen birth registration (BR) and link BR to distribution of immunization cards during perinatal and neonatal care contacts. The multi-country evaluation of immunization's Reach Every District (RED) noted one common weakness was the lack of maternal and neonatal registration, recommending that: "More active use of community volunteers to identify these women and children would facilitate the ability of health facilities to locate and serve their clients "[27]. Recent innovations, including use of Rapid SMS to alert local authorities of a new birth and trigger birth registration and distribution of immunization cards is being explored in several contexts [29, 39].

How might increasing resilience link to equitable coverage for immunizations? One approach is using the opportunity of new vaccine introduction for either pneumonia or rotavirus as an advocacy platform for increased attention to increasing community resilience. This could be achieved by addressing demand side enablers of resilience such as promotion of hand-washing, and supply-side enablers such as support for actions to increase access to safe water and sanitation.

Conclusion

Health system strengthening efforts should be viewed as an integral part of the mechanism for delivery of required immunization services, not as a complementary element to this. The objectives and focus of health system strengthening efforts are built on putting in place the necessary platform to assure the delivery of required program interventions in an efficient, equitable and effective manner. The health system strengthening efforts are therefore not an end in themselves, but rather a means to an end. Health System strengthening remains an integral part of the efforts towards UHC and attainment of the SDGs.

Health Systems, UHC and the SDGs



While the immunization program is specifically interested in a selected set of elements of the health system, the functionality of the whole system is needed, for the program to assure the elements they are interested in are available and functional. Therefore, as a program, we should be interested in ensuring full system functionality. This is through three mechanisms: (1) making direct investments; (2) working with similar programs to make combined investments, or (3) becoming an advocate for making of required investments. The approach the immunization program takes is country dependent, and should be driven by evidence in terms of impact on the overall immunization goals, and feasibility. A system diagnosis would assist the country to understand the gaps in the system and their potential impact on immunization outcomes. A health workforce (HW) gap may be addressed by direct recruitment of HWs in one country, or by advocating with Finance for more HW recruitments in another.

Having a resilient, fit for purpose and responsive health system should be the goal that immunization programs support across all countries, as this is what will assure delivery of immunization program outcomes in a sustainable manner. Selective investments, with little understanding of the state of the system and the environment within which it is operating will not give the kinds of goals the program is seeking. The immunization program delivery model needs to take cognizance of this, for it to attain Universal Coverage with required antigens. Attainment of its goals requires a concerted effort that looks into what kinds of access, quality and service demand targets the health system needs to achieve, and then strategize on how to facilitate attainment of these targets through assuring presence of needed investments in the different elements of the health system.

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ANNEX 1: A REVIEW OF DELIVERY SCIENCE

What is delivery science?

Delivery science includes research and training to understand and improve health care delivery. Health-related implementation research is the use of science to study practices in routine clinical care and public health systems in order to improve the quality and equity of health care. It also includes the study of factors that influence health care professionals and organizations and the factors influencing users of health care services, thus covering demand and supply. Implementation research often involves impact research, which includes research aimed at understanding what happens during the process of implementing a change in policy, program, or practice, and intervention studies, which are designed to compare different approaches to implementing change.

Robert Kern have defined “The science of health care delivery focuses on how patients actually receive care. From using engineering principles to determine the most efficient way to schedule patient appointments to research focusing on the most successful, cost-effective means for delivering treatment, this discipline's aim is to enhance the patient's experience with health care by improving quality, outcomes and cost. The main goal of science of health care delivery is to analyze, evaluate and implement care delivery models that improve value for patients (combining data analysis, engineering principles and health care delivery research)” The science of health care delivery applies innovative science and data to evaluate the quality, safety and value of health care globally, and improve real-world experiences for patients. The science of health care delivery is useful to address how to use data science and operational research methods to develop and evaluate new models of care; improve patient care and population health by studying, developing, and integrating clinical practice with the patient's community and translate research by applying tools and methodologies to create a learning health care system.

The current review of literature shows that health care delivery science is one of missing piece in health system area. WHO is mandated to support its Members states to be able to deliver safe, appropriate, effective, and quality services to the population through an integrated, patient centered health care approach. In this current context delivery science as transversal approach is an important strategy to address complexity of delivering health care in a way that keeps people healthy and provides quality health care at low cost. One of the current challenges is how to ensure access to services to more people, specifically the most marginalized and vulnerable and those living in remote areas.

There are vast amounts of resources being funneled into global health work, such as vaccines, primary health care, drug therapies, maternal and child health care, and basic surgery. Specifically for vaccines, WHO and international community has produced a lot of evidence and guidance on how to better deliver vaccines at the health care contact points (fixed or mobile). However, the greatest constraint is not

the availability of equipment, medicine, etc., but rather the way it is being delivered to those who need them most.

Why it is important?

- Delivery science is important to address the complexity of delivering health care and sustain high quality health care at low cost
- To address a range of implementation challenges, including complex processes, inefficient use of resources, inequitable allocation of resources, and supply and demand barriers to scaling-up and sustainability
- To improve the quality and equity of health care
- To support the development of multidisciplinary approach, encompassing both quantitative and qualitative approaches
- To develop mechanisms to compare different approaches to the delivery of global health services and their level of effectiveness, affordability and equity considerations
- To provide high accessibility of medical interventions including vaccines
- To address systems weaknesses in immunization programs
- Implementation research based on delivery science has an important role to identify challenges and successes, the possible impact of improving delivery (efficiency, efficacy, quality, costs, equity and sustainability issues)

What are the main challenges?

- Limited attention has been provided to the science of implementing interventions effectively and equitably in many parts of the world.
- Information and evidence is fragmented and focus only on some specific interventions rather than on the broader services as part of the health systems.
- A major proliferation of global health initiatives that continues to operate in isolation, at national level
- More research, case studies, anecdotes and other mechanisms of documenting experience are needed on issues of health care delivery including to demonstrate how to reach and benefit people
- Lack of information on the delivery of clinical interventions, target populations and lack of relevant health infrastructure, also they are incomplete at times, not tested and are not suited for the community
- Advocate bilateral and multilateral agencies including GAVI to support implementation research and the adequate use of delivery science to have better integration of vaccines delivery into the health system
- Absence of political will to invest on the science of health care delivery
- Lack of training on how to use delivery science to improve quality of care
- Harmonizing/ integrating the various area of delivery sciences
- Inadequate consideration of country and community context in delivering interventions
- - the lack of consideration for the voice of communities and citizens and specifically marginalized people
- The challenges are not just finance, supply and logistics but as well to consider enough in the large picture others issues such as community's voice, trust, communication, education, attitude, history, religion, politics and power.

It is evident that the traditional approach will not provide us with solution to complex issues that occur within the health system. We therefore, need new approaches. Various people have tried to explore these issues using various approaches using science and tapping on explicit and implicit knowledge of individuals and communities.

- There is an overall lack of consideration for all the elements of health systems (or integrated approach) and the context of their application.

Background and role of delivery science

A World Health Organization May 2008 consultation report entitled **"Maximizing Positive Synergies between health systems and Global Health Initiatives"**[1] reports on this process. The document carefully outlines the need for this type of solution, the knowledge-gathering process and coordination required to achieve it, and offers examples of existing work that is being done in the area. Within the larger framework of global health, this concept is part of the goal of developing a "science of delivery," and addressing the proliferation of global health initiatives that operate in isolation.

As per Kim et.al. (2013), it is difficult to address the ever-increasing, unsustainable costs of health care without getting to the foundation of how health care is provided. Nor can we achieve the social and moral goals we share – care that is safe, appropriate, effective, people centered and integrated in every community – without rethinking and redesigning delivery. Real improvements require a multidisciplinary approach that will bring the best minds to focus on the problem. Experts in management, systems thinking and engineering, sociology, anthropology, economics, medicine, health policy, and other fields must join together to fix the delivery system." In addition, the authors have provides detailed information on the global role of health care delivery science, for example; the need to redefine the global health care delivery; ensure access to appropriate information to both population and individual level; Improve understanding of harmful practices associated with delivery science; an opportunity to understand and reduce wastage and improve efficiency; need to scale up integrated service delivery and strengthen district health systems.

Today, part of the reason for delivery failure is due to the lack of health infrastructure in many low and middle income countries. Due to this, the global health community faces an unprecedented challenge of transferring vast amounts of resources to individuals, often in rural and remote locations, with little-to-no infrastructure to work through. Several steps exist in the process of achieving successful health outcomes: the discovery of a drug or intervention, its development and production, and lastly, its delivery. It is this final link in the chain that poses the most formidable challenge to

[1] World Health Organization. (2008). Maximizing Positive Synergies between Health Systems and Global Health Initiatives: Report on the Expert Consultation on Positive Synergies between Health Systems and Global Health Initiatives. *Geneva, Switzerland: WHO*.

the success of global health endeavors. It is very well recognized that this is not a stand alone problem but rather a complex one as it falls within the health system, which is complex. In other words, anything that falls within the health system has to be dealt with through a wider lens. WHO therefore recommends that one of the ways to reduce the difficulties related to health care services should be to ensure that all services are provided through “an integrated, people centered service delivery approach”. WHO has recently developed the strategy on Integrated people-centered service delivery, which should be widely shared with all entities involved in providing health care services, including, countries, NGOs, and policymakers what are the current best practices, cases studies and lessons learned in delivery science. Having said that, this area still needs to be explored and researched further, including the levels of effectiveness, affordability and equity issues among many.

Vision and mission of WHO in delivery sciences

In WHO, health care delivery research build from the results of operations research, participatory action research, management science, quality improvement, implementation science and research, and impact evaluation and requires flexible designs to account for the changing contexts and interventions. It addresses a range of implementation challenges, including complex processes, inefficient use of resources, inequitable allocation of resources, and supply and demand barriers to scaling-up and sustainability.

For vaccine and immunization, the Global Vaccine Action Plan (GVAP) highlight the importance of improving delivery of immunization services to achieve its goals. More specifically, the GVAP request members states, WHO and all others stakeholders to improve the logistics and the delivery of services to the hard to reach population. This implies WHO and others to have better knowledge about the issues related to unvaccinated and under-vaccinated children, delivery science are therefore crucial element. WHO has encouraged the operational research on delivery of vaccination, the logistic of vaccination and the demand and hesitancy from communities and individuals.

Activities of WHO in delivery sciences at global, regional and country levels

In the context of vaccine and immunization, WHO has been focusing mainly on implementation research as an important step towards achieving an increase in vaccine coverage and the uptake of new vaccines. Implementation research is highly complex and requires participation of stakeholders from diverse backgrounds to ensure effective planning, execution, interpretation, and adoption of research outcomes. It is highly contextual and depends on social, cultural, geographic, and economic factors to make the findings useful for local, national, and regional applications. Implementation research has an important role in accelerating the introduction and sustained use of vaccines in older children and adults.

The science of implementing interventions, in an effective, efficient, and equitable manner has received inadequate attention, in many regions of the world, where research capacities are also limited.

Tools provided by WHO

The strategic framework for vaccine implementation research have been defined within the WHO Initiative for Vaccine Research (IVR) Strategic Plan 2010–2020

The WHO Research for Health Strategy adopted by the 2010 World Health Assembly builds on the Mexico Ministerial Summit (2004) and the Bamako Global Ministerial Forum on Research for Health (2008), both of which reiterate the importance of focusing on research to promote knowledge translation.

At global level

Implementation research have been used by WHO specifically for annual Vaccination Week (now expanded globally), the elimination of rubella and congenital rubella syndrome, measles eradication, the introduction of vaccines against rotavirus, human papillomavirus, and influenza, and the ProVac Initiatives. Taken together, these vaccine delivery-related initiatives have led to the deployment and provision of lifesaving vaccines in this geographic region.

Vaccine and immunization area have been able through the integration of others interventions into the health system to take in consideration broadly principal components of health systems: structures, equipment and supplies, policies (technical priorities, financing), people (their numbers, distribution, and skills mix), and processes (how people function within the system and in relation to other sectors). Today many efforts are focused on how these components articulate among each another and the communities in which they are based, their effectiveness, and opportunities for modification are also framed by the social and political context in which they have evolved.

At regional level

WHO African region have been able to implement the initiative African Vaccination Week (AVW) lead by the Member States from Africa, which aimed at promoting vaccination and ensuring equity and access to its benefits. The initiative has proven to be particularly effective in reaching populations with limited access to regular health services as well as providing an opportunity to integrate other interventions with immunization services. Integration of other interventions with immunization during AVW, in the African Region is common and has shown potentials for improving immunization coverage, as this dedicated period is used both for catch-up campaigns and periodic intensified routine immunization. While its impact may call for further examination, it is a potential platform for integrated delivery of health interventions to people with limited access to regular health service.

At country level

WHO usually plays catalytic role with the partners to implement research activities in the area of service delivery. For examples, in its “reach every district, reach every community” through reference strategy, WHO encourages countries and partners to identify the challenges behind low coverage for specific population.

Delivery science research results at country level identified several issues related to low coverage

Importance of political will

The study of regional inequity and vaccine uptake in Malawi revealed the presence of clusters of under-vaccinated children, leading to increased vulnerability during outbreaks of vaccine-preventable diseases. This study also suggested that there is substantial potential for political intervention to improve the current state of immunization

Importance of taking into consideration local context and to ensure a quality monitoring and evaluation system

The strength of childhood immunization in South Africa comes from having a framework for intervention that not only is strong but that requires implementation to be tailored to local circumstances and accompanied by high-quality monitoring and evaluation

Importance to retain skilled staff at rural areas

Experiences in Mali indicate that sustained immunization efforts will require improvements in staffing, financing, and delivery-related guidelines to ensure the presence of skilled staff at the periphery

An experience from one state of Sudan, revealed that the government must make greater efforts in funding, provision of skilled manpower and delivery mechanism to achieve higher rates of vaccination in rural areas.

Importance of continuity of health care services

In a study in Burkina Faso that investigated rates of coverage and determinants of complete vaccination in rural areas, researchers found that continuity of health care services from prenatal care to institutional delivery created families' loyalty to health services and was closely associated with communities' rates of child vaccination

Importance of immunization intervention package

An immunization intervention package (including service schedule, training for service providers on valid doses and management of side-effects, a screening tool to identify immunization needs among clinic attendants, and an immunization support group for social mobilization) was found to dramatically improve child immunization coverage in urban slums of Dhaka, Bangladesh

Importance of system thinking approach

A recent study have highlighted that managing through health systems, and not being overly reliant on committees, will be more beneficial and expand the reach of immunization and maternal and child health care services in developing countries. Careful characterization of health system problems within a specific country context can generally improve the efficiency of delivery and access.

Examples of case studies are related to the introduction of new vaccines for low- and middle-income countries

A case study from six low resource setting, on the impact of introducing new vaccines on the health system, showed that the new vaccines were viewed positively and seemed to integrate well into existing health systems. The introductions were found to have had no impact on many elements within the building blocks framework. Despite many key informants and facility respondents perceiving that the new vaccine introductions had increased coverage of other vaccines, the routine data showed no change. Positive effects perceived included enhanced credibility of the immunization programme and strengthened health workers' skills through training. Negative effects reported included an increase in workload and stock outs of the new vaccine, which created a perception in the community that all vaccines were out of stock in a facility. Most effects were found within the vaccination programmes; very few were reported on the broader health systems. Effects were primarily reported to be temporary, around the time of introduction only.

The case study from the United Republic of Tanzania on costing nationwide HPV vaccine delivery using the WHO Cervical Cancer Prevention and Control Costing Tool show when a country expand its immunization schedules with new vaccines such as the HPV vaccine, it faces initial cost to fund critical pre-introduction activities, as well as incremental system costs to deliver the vaccines on an ongoing basis. In anticipation, governments need to plan ahead for non-vaccine costs so they will be financed adequately. Existing human resources need to be re-allocated or new staff need to be recruited for the program to be implemented successfully in a sustainable and long-term manner. The financial delivery costs of nationwide HPV vaccination are higher than those of infant vaccines and can be substantial in resource-poor settings since it requires building up new delivery channels (like more transport of vaccines and health workers and more intensive IEC activities).

The case study on the contribution of primary care to health and health systems in low- and middle-income countries. It is critical review of major primary care initiatives have showed there is also evidence that primary care programs have reduced child mortality and, in some cases, wealth-based disparities in mortality. Lastly, primary care has proven to be an effective platform for health system strengthening in several countries. Future research should focus on understanding how to optimize the delivery of primary care to improve health and achieve other health system objectives (e.g., responsiveness, efficiency) and to what extent models of care can be exported to different settings. The majority of primary care programs had multiple components from health service delivery to financing reform to building community demand for health care. Although given this integration and the variable quality of the available research it was difficult to attribute effects to the primary care component alone, we found that primary care-focused health initiatives in low- and middle-income countries have improved access to health care, including among the poor, at reasonably low cost.

Pre-empting and responding to vaccine supply shortages
SAGE April 2016
EXECUTIVE SUMMARY

Introduction & situation

Vaccine Security, defined as the "sustained, uninterrupted supply of affordable vaccines of assured quality" [1], is recognised as a key component of successful national immunisation programmes. This area is getting more and more attention at all levels, particularly as several countries are having difficulties accessing some vaccines in the quantity they need.

Indeed, over the past couple of years, many countries, across regions and income groups, have reported shortages of vaccines. WHO EURO conducted a survey on shortages in September 2015 to which 77% of countries[2] replied that they had experienced a shortage of supply[3] of at least one vaccine since the beginning of the year. In the Americas, PAHO reported that in 2015 the availability of yellow fever vaccine was just enough to cover 40% of the regional demand.[4] In December 2014, UNICEF expected the mismatch between its demand and supply awards for the BCG vaccine to reach a deficiency of 71 million doses.[5] The same issue has been reported for several vaccines, many considered traditional vaccines, including yellow fever, BCG, DTP, acellular pertussis (aP) containing vaccines and IPV.

Shortages of vaccines for outbreak response, such as meningococcal C and W containing vaccines have also been reported. In July 2015, WHO sounded the alarm over insufficient stockpiles of vaccines as the threat of epidemics caused by serogroups W and C appeared to be increasing. Meningitis C was identified as contributing to a meningitis outbreak in Niger in 2015.[6]

Other biological products, such as snake antivenom and diphtheria antitoxin, have also been in short supply for several years.[7,8]

These shortages sometimes cause critical disruptions in timely immunisation services. Based on JRF data, in 2014 50 countries reported stockouts of two vaccines at national level for at least one month. More concerning is that in 33 countries[9], district level stockouts led to an interruption of vaccination services. While stockout issues have been reported across all income groups, Middle Income Countries (MICs) seem particularly affected: 60% of all 50 countries reporting national level vaccine stockouts in 2014 were MICs. Also, more upper MICs and higher-income countries reported national level stockouts in 2014 than in 2013.[10]

Countries are therefore urging WHO to provide more information and assistance in order to better understand the vaccine supply situation, mitigate the effects of current shortages and prevent future ones. However, a comprehensive and global view of vaccine supply as well as vaccine shortages is missing, particularly for vaccines not supported by external development assistance.

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[1] UNICEF definition, http://www.unicef.org/supply/files/RFP_501959.pdf.
[2] 20 out of 26 countries that returned the questionnaire.
[3] Defined as "not being able to access the appropriate number of doses at the national level for planned activities".
[4] PAHO revolving Fund, Vaccines Supply Shortages, Challenges & Opportunities. DCVMN 16th International Annual General meeting. Bangkok, Thailand. October 2015. Accessible at: http://www.dcvmn.org/IMG/pdf/dcvmn_2015_paho_presentationv2_for_publishing.pdf.
[5] UNICEF Supply Division, BCG vaccine: Current Supply & Demand Outlook. December 2014. Accessible at: http://www.unicef.org/supply/files/BCG_Supply_Status_December_2014.pdf .
[6] WHO, Rapidly growing outbreak of meningococcal disease in Niger. May 2015. Accessible at: Rapidly growing outbreak of meningococcal disease in Niger.
[7] WHO, WHO highlights critical need for life-saving antivenoms. May 2010. Accessible at: http://www.who.int/mediacentre/news/notes/2010/antivenoms_20100504/en/.
[8] ECDC, Diphtheria case highlights shortage of antitoxin in EU. June 2015. Accessible at: http://ecdc.europa.eu/en/press/news/_layouts/forms/News_DispForm.aspx?ID=1239&List=8db7286c-fe2d-476c-9133-18ff4cb1b568&Source=http%3A%2F%2Fecdc.europa.eu%2Fen%2Fpress%2Fnews%2Fpages%2Fnews.aspx.
[9] Corresponding to 86% of countries that registered a district level stockout.
[10] GVAP Secretariat, Global Vaccine Action Plan Monitoring, Evaluation & Accountability, Secretariat Annual Report 2015. 2015. Accessible at: http://www.who.int/immunisation/global_vaccine_action_plan/gvap_secretariat_report_2015.pdf.

The importance of vaccine security and access to timely supply was highlighted at the 68th World Health Assembly (WHA) in May 2015, with the adoption of a resolution on the Global Vaccine Action Plan (GVAP) that urged Member States to *"improve and sustain vaccine purchasing and delivery systems in order to promote the uninterrupted and affordable safe supply of all the necessary vaccines"*.[11] The resolution also urged WHO to address factors that can detrimentally impact vaccine availability, through technical support to countries and specific programmes supporting and monitoring accessibility of quality vaccines at affordable prices.

Vaccines are not the only medical products at risk of shortages, and several medicines on the WHO Model Lists of Essential Medicines[12] have also been in short supply in recent years. There is insufficient information to measure the magnitude of the problem at global level, but at national level, data collected have shown the depth of the issue. In the US, for instance, drug shortage reports have listed 300 products in shortages in 2013, double that registered in 2010.[13] Given the necessity to maintain access to essential medicines, a report was presented at the WHO Executive Board in January 2016[14], detailing actions that could be explored at national and global levels in order to better pre-empt and respond to drug shortages.

Shortages versus stockouts

There are no well-established definitions of vaccine shortages. For the purpose of this work, and in order to distinguish between "shortage" and "stockout", the following definitions have been used:

- Vaccine shortage: there is a vaccine shortage when a vaccine cannot be obtained by a country in sufficient amount to meet its needs. The lack of vaccine availability can be global (several countries impacted) or local (one country cannot acquire the volume it needs).
- Vaccine stockout: there is a stockout of vaccine when stocks at the national or district levels have been depleted.[15]

This means that a shortage may or may not lead to a stockout, if the country has enough doses in stock to bridge the lack of supply for some time. Stockouts of vaccines are also not necessarily related to a vaccine shortage, but may also be caused by poor use of available doses within the country (e.g. poor stock management or supply chain issues). According to a root cause analysis conducted by UNICEF in the 90 countries procuring vaccines through the Supply Division in 2014, only 10% of stockouts were due to global shortages.[15]

Main identified causes behind vaccine shortages

There are several causes behind shortages and they may vary from one vaccine to another and from country to country. They can be divided into three categories:

- Supply: Supply factors relate to the production of vaccines as well as market conditions (such as the number of products available and the number of manufacturers active on each vaccine market). Supply factors influence availability of vaccines.
- Demand: Demand factors relate to the flexibility and predictability of demand. Demand predictability relies on the capacity of a country to accurately forecast its demand and to have the appropriate measures in place for this demand to materialise. Demand flexibility relies on processes being in place to ensure that a country is able to secure the supply it needs. Demand factors influence access to timely supply.

[11] 68th World Health Assembly 2015, Resolution WHA68.6, Global Vaccine Action Plan. May 2015. Accessible at: http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R6-en.pdf .
[12] Lists are accessible at: http://www.who.int/medicines/publications/essentialmedicines/en/.
[13] International Pharmaceutical Federation (FIP), Report of the International Summit on Medicine Shortage. Toronto, Canada, June 2013. Accessible at: http://apps.who.int/medicinedocs/documents/s20979en/s20979en.pdf .
[14] WHO Executive Board, Addressing the global shortages of medicines, and the safety and accessibility of children's medication, report by the Secretariat. EB138/41. Geneva, Switzerland. December 2015 http://apps.who.int/gb/ebwha/pdf_files/EB138/B138_41-en.pdf .
[15] GVAP Secretariat, Global Vaccine Action Plan Monitoring, Evaluation & Accountability, Secretariat Annual Report 2015. 2015. Accessible at: http://www.who.int/immunisation/global_vaccine_action_plan/gvap_secretariat_report_2015.pdf.

- Information: Information factors relate to the lack of information available at the global level on supply and demand, which may contribute to a misalignment of supply and demand. Information factors influence the quality of communication and data availability to take sound, informed decisions from both the demand and supply sides.

More information on these causes is available in Annex 1.

Actions taken to mitigate impact of vaccine shortages and pre-empt future shortages

As there is no centralised information available on vaccine shortages and the mechanisms that countries have set up to cope with them, it is difficult to have a bird-eye view of the situation. Some specific information and data-collection exercises conducted in Europe have permitted a clearer view of actions taken at country level. In this area, responses are usually very reactive and intend to mitigate as much as possible the impact of short supply on service delivery. The current shortage situation is also generating ideas for longer term actions that countries, groups of countries and global organisations could set up to better respond to and pre-empt these shortages.

Actions by countries

In some countries and groups of countries, work has been undertaken to respond to and prevent shortages, sometimes with the support of regional or international partners. However, most countries find themselves unable to cope with and respond to these shortages. In June 2015, the European Technical Advisory Group of Experts on Immunisation (ETAGE) stated that "some Member States appear to have very limited or inadequate mechanisms in place to respond to fluctuations in vaccine supply, and little or no resilience in the face of vaccine supply interruptions. Further efforts are urged to support these countries in developing appropriate mechanisms to ensure sustainability of vaccine supplies and avoid vaccine stockouts".[16]
Some countries are taking action to limit the impact of shortages. For instance, since 2015, nine Member States of the European Union / European Economic Area (EU/EEA) have adjusted their immunisation policies due to shortage of the aP vaccine. Measures have included[17]:
• Temporary suspension of the primary immunisation doses (e.g. Bulgaria)
• Changes to the primary immunisation schedule age of dose administration (e.g. Romania, Hungary)
• Modification of the vaccine formulation used as pre-school booster (e.g. Belgium, France)
• Delayed introduction of a new antigen in the primary immunisation schedule (e.g. Norway)
• Prioritisation of vaccine formulation for the primary immunisation schedule(e.g. Spain, Sweden)
• Use of acellular pertussis-containing vaccines not originally authorised in the EU

Actions by groups of countries & regions

Countries with existing regional common institutions are exploring possibilities to reinforce vaccine security at the regional level.

In the Americas, the PAHO Revolving Fund has become an example to other international organizations and WHO regions of an effective mechanism to ensure an uninterrupted supply of affordable, quality vaccines in the complex global vaccine market.

In the Association of Southeast Asian Nations (ASEAN), Member States are working together to explore opportunities for cooperation to improve vaccine security in the region. Several workshops

[16] WHO, meeting report of the 15th meeting of the European Technical Advisory Group of Experts on Immunisation (ETAGE). Copenhagen, Denmark. September 2015. Accessible at: http://www.euro.who.int/__data/assets/pdf_file/0008/295559/ETAGE-2015-Report.pdf.
[17] European Centre for Disease Prevention and Control. Shortage of acellular pertussis-containing vaccines and impact on immunisation programmes in the EU/EEA – 8 October 2015. Stockholm: ECDC; 2015.

are being organised with Member States to assess feasibility and potential impact of areas such as "collaborative systems", "human resources development", "common price policy & pooled procurement" and "improved communication & coordination". [18]

In the European Union, the Commission, in cooperation with the European Centre for Disease Prevention and Control (ECDC), the European Medicines Agency (EMA), and WHO, is working with Member States to identify possible policy interventions in order to address problems related to vaccine supply. Measures proposed are *inter alia* aiming at strengthening mutual assistance of Member States in case of urgent vaccine needs or strengthening vaccine supply infrastructure in Member States.
More information on the work done in the European Union is available in Annex 2.

Actions by global partners

Several actors at the global level are implementing solutions in a collaborative manner. Activities include mitigation efforts, but also procurement planning, information-sharing mechanisms and longer term actions to support healthy markets.

Partners, including WHO, PAHO and UNICEF, are supporting countries in their mitigation efforts and working collaboratively to find adapted solutions. For instance, in 2015 WHO and UNICEF worked together to increase the supply base of BCG, through fast-tracking prequalification of a new product and through working to secure additional quantities from existing manufacturers. As a result, UNICEF is expecting supply to be sufficient in 2016 to meet both suppressed 2015 demand carried over to 2016, as well as total forecast demand through 2016-2018.[19] The WHO Prequalification team[20] has also worked with individual countries to support fast-tracked national registration of new products (e.g. BCG in South Africa).

Longer-term activities vary from one organisation to another, spanning from activities targeting demand factors (policy, introduction, forecasting, vaccine delivery, supply management and tendering) to activities on supply factors (industry incentives, product development and market strategies) and information & communication factors. However, many activities implemented by international organisations focus on very specific groups of countries, with markets targeting Gavi-countries receiving the most support. Indeed, partners collaborate through Gavi, the Vaccine Alliance, to ensure that needs of the poorest countries are correctly matched by an adequate supply of vaccines. With that aim, the Alliance plays an important role in strengthening vaccine markets. For instance, efforts to strengthen the DTwP-HepB-Hib market have contributed to the "healthy market" that exists today, with a good supplier base of eight manufacturers with prequalified products.[21]
On information sharing, UNICEF offers comprehensive supply and demand information for the products and countries it serves, through "Market Updates" regularly published on the UNICEF website.[22] However, a complete and centralised view of global supply and demand for all vaccines and all countries does not exist at this stage.

More information on long-term actions and areas of work of several global key partners is available in Annex 3.

[18] ASEAN. Executive Summary: Workshop among ASEAN Countries on Opportunities for Regional Vaccine Security. Phuket, Thailand. October 2014.
[19] UNICEF, Q and A: Update on BCG vaccine market – February 2016. Accessible at: http://www.unicef.org/supply/index_90306.html.
[20] WHO system for the prequalification of vaccines. Accessible at: http://www.who.int/immunization_standards/vaccine_quality/pq_system/en/.
[21] List of WHO prequalified vaccines accessible at: https://extranet.who.int/gavi/PQ_Web/ .
[22] UNICEF, Vaccines Supply and Market Overview. Accessible at: http://www.unicef.org/supply/index_vaccines.html .

Annex 1: main identified causes behind shortages[23]

CATEGORY	SUB-CATEGORY	FACTORS	DESCRIPTION & EXAMPLES
SUPPLY	Production issues	Batch failures and high risks linked to biological products	• Biologics are natural products so production with consistent accuracy is more complex than for manufactured drugs, leading to a higher risk of production failure (including "out of specification" batches). Variability of in-vivo control testing may have an impact on lead time and/or increasing batch losses.
		Complex & long production processes and quality controls	• Long production and capacity lead times: up to 1-2 years per lot and 3-5 years for a new facility. • Tight quality controls (QC): complex production process also relates to complex QC testing, which in some cases may delay availability or rapid access of vaccines. The weight of control steps can take up to 70% of production time. • Regulatory systems: national regulatory agencies (NRAs) in producing countries are not all functional (36 out of 44 countries in 2014 had a functional NRA). Regulatory requirements may vary by country. Sometimes also a high workload on the NRA can delay availability of supply (e.g. in India).
		Tight production planning	• Leaner production practices ("just-in-time" to reduce inventory and waste): leads to stronger consequences when something fails on the production line and limits the capacity to answer to rapid increases in demand. Production is also more at risk in case of decreased availability of quality raw material or substances. • Scaling up production: complex production process makes rapid scaling up of production difficult. • Product prioritization: if a manufacturer decides to switch a production line from a vaccine to another (e.g. to respond to an outbreak), there is a risk that another vaccine may not be produced (e.g. bottlenecks at filling or packaging stages). • Renovation of facilities: they are costly, take time and interrupt production. It may not be possible to produce enough doses in advance to bridge the time until the line becomes productive again. • *Example of seasonal influenza*: demand in Europe is not as high as expected, leading manufacturers to consider lowering their production. However, in case of an outbreak, capacities to respond will be reduced .
	Limited supplier base	Entry barriers (high sunk costs, R&D investments, technical know-how, GMP, investment risks, …)	• High sunk costs: building new production lines and acquiring appropriate technical equipment is very expensive. New plants can cost several hundred millions to build. • R&D investments: R&D investments are costly. E.g. R&D costs for rotavirus vaccines have been estimated at $150-508 million for Merck and GSK's products. These amounts do not account for other failed R&D investments. • Technical know-how: to maintain quality of production, it is important that manufacturers follow Good Manufacturing Practice (GMP – latest WHO guidelines on GMP for biological products were updated in October 2015). In some countries (particularly developing countries), there may be limited capacity to develop, enforce and sustain further GMP.
		Decisions based on product and market	• Market segmentation (developed vs developing countries): manufacturers from developed countries tend to focus efforts on expensive new vaccines and manufacturers from developing countries to focus more on traditional vaccines. • Pressure on price and the issue of sustainability: manufacturers may decide not to invest (e.g. to renovate manufacturing

[23] Note that this is a working document that is still under development and review.

SUPPLY		attractiveness (e.g. profitability, certainty, …) and ROI	facilities) in products with high uncertainty or low Return on Investments (ROI). Some manufacturers find themselves unable to compete with manufacturers located in places with very low costs, including low labour costs. Driving prices down too much may lead certain manufacturers to take the decision to exit the market. • Competing against drugs: in large multinationals, vaccines may have to compete against drugs for attention and resources and need to prove that they are a good investment.
		Market strategies	• Preference for most profitable markets: some products might be developed to target high-income markets first and may not be adapted to low income settings (e.g. to be used out of the cold chain). In case of limited production available, manufacturers may decide to focus first on high-income markets. In the case of BCG, allocation of production to immunisation programmes may enter in competition with use as a bladder-cancer treatment. • Unknown political incentives: they may affect decisions to allocate doses to a country rather than another. • Cannibalisation between vaccines: when newer combination vaccines enter the market, manufacturers may decide to redistribute production capacity to the newest vaccine and phase out the older vaccine, thus reducing the supply base of the older vaccine for countries that have not switched to the newer combination (eg. introduction of DTwP-HepB-Hib reducing availability of DTwP ; short supply of DTaP-Hib-IPV in 2015 while the hexavalent remained available) .
		Mergers & acquisitions (concentration)	• Concentrated markets with limited number of players: the nature of vaccine manufacturing costs, supply, and risk generates long-run market equilibrium with one or very few vaccine suppliers at any point in time. In markets with a limited number of manufacturers, a reduction in produced quantity from one manufacturer may quickly lead to "domino shortages", as demand can only shift to a limited set of alternative products. These products may not be available in sufficient quantities to cover the resulting increase in demand (e.g. HepA vaccines in France in 2015-2016, with "domino shortages" of Havrix (GSK), then Avaxim (Sanofi Pasteur) and then putting Vaqta 50 (Merck) at risk of shortage as well). • Reduction in number of producing countries: as the market concentrates, the number of producing countries decreases (from 60 in 1990 to 44 in 2014). This market situation also limits profit possibilities for small manufacturers who are not strong enough to compete with large multinational manufacturers for market shares.
		Local production	• Relying on local production: several countries rely on local production for their local needs of traditional vaccines. Relying on small local production plants may increase the risk of shortages for the country if a production issue occurs or if the demand suddenly increases (lack of flexibility to respond to fluctuation in production or demand). • Investments in public sector manufacturing may be more at risk of sustainability: these investments are more likely to be at risk of sustainability as they often survive on subsidies. In the past, out of 11 countries with public and private investments in local manufacturing, only 2-3 have been considered successful. • *Example of BCG*: for many years, production of BCG has relied on local manufacturing. For instance, there are currently 4 manufacturers of the DCVMN (Developing Countries Vaccine Manufactures Network) producing BCG, with only 1 aiming at the global market with a prequalified product (Serum Institute of India) and 3 publicly supported companies with local capacity only (production capacity < 10M doses).
DEMAND	**Little demand flexibility**	Safety concerns	• Product quality: countries tend to prefer products that are WHO prequalified or that are produced and/or used in high-income countries (HICs). In 2015, 95% of vaccines registered by countries in the V3P database were either WHO prequalified vaccines or were produced in HICs.

DEMAND			• Confidence and good relationships with one manufacturer: when a country trusts a manufacturer it may be inclined to continue working with this manufacturer , especially if there has been no safety issue with the product(s) purchased. Relying on only one manufacturer creates dependence and increases the risk of shortage if the manufacturer cannot deliver the product (production issues, cessation of production, …). Reactivity to respond to a shortage is reduced.
		Inefficient and un-harmonized registration procedures	• Complex registration procedures: countries asking for stringent procedures (e.g. high fees, lengthy paperwork, translation, local clinical trials, inspection, …) might deter manufacturers from registering their products, particularly in small or less attractive markets/countries... Varying product specifications across countries also limits supply flexibility. • Lack of functional NRAs: in 2015, on 194 WHO Member States, only 60 had a functional NRA. • Lengthy registration processes: impact expedited access to vaccines. • Few products registered: issues with registration processes may partially explain the fact that they are few products registered in each country at any point in time.
		Limited evidence on product interchangeability	• Limited interchangeability between products: traditional vaccines may be used interchangeably but in general there are few studies showing interchangeability of vaccines. Therefore, once a product is added to the immunisation programme it is not easy for the country to switch to another product. It limits access to alternative products if one product becomes in short supply.
		Single award tenders	• Single-source procurement: tenders are often awarded to only one manufacturer/product. It means that a country rely on only one supplier for each vaccine, which increases the risk of shortages if availability of this product decreases. It also increases delays to find an alternative solution if a shortage occurs. • *Example of UNICEF on multiple-award tenders*: UNICEF clearly states in its procurement principles that it procures from multiple suppliers for each vaccine presentation in order to strengthen security of supply.
		Low elasticity of demand resources	• Budget constraints: immunisation budgets are usually fixed at the national level and may not be extended to cover for economic factors impacting the purchase of vaccines, such as volatile exchange rate. This can have dramatic consequences for access (e.g. in South Africa, the Rand lost more than 50% of its value against the US dollar between 2011 and 2015). • Lack of flexibility of donor money: if the demand was not forecasted correctly it might be difficult to get extra financial support for missing doses. Donor-funded demand can be complex and therefore limits flexibility.
	Lack of demand predictability	Weak country decision-making	• Lack of strong decision-making systems: paths leading to decisions are not always well understood and clear. Lack of strong decision-making systems may impact timely and evidence-based immunisation policy making. • Lack of functional NITAGs: only one third of non-Gavi MICs have a functional NITAG (20 out of 59 countries with data in 2014).
		Poor political commitment & financing	• Poor political commitment: in some cases, insufficient political will translates into inadequate national financing as well as inefficient use of available resources, which may affect the maintenance of immunisation services as well as new vaccine introductions. • Allocation of financial resources to support immunisation: according to a root-cause analysis conducted by UNICEF in 2015 on 90 countries procuring through UNICEF SD, 39% of stockouts of vaccines were due to funding delays.
		Vaccine hesitancy	• Vaccine hesitancy: it is becoming a growing concern across regions and income groups. It is often linked to a lack of

DEMAND			confidence in vaccines and reduces demand predictability. • *Example of the United States*: in 1999, the rationale behind the decision to minimize the use of thimerosal in some vaccines was not well communicated. As a consequence, public confidence in vaccines decreased, which led to increased vaccine hesitancy and refusal to vaccinate. The subsequent decrease in coverage may lead to outbreaks, such as the measles outbreak in the United Sates in 2014-15. Reactions to the outbreak, in turns, led to a rapid and unpredictable increase in demand for the measles vaccine.
		Weak procurement systems (incl. anticipation and planning, forecasting, budgeting & tendering)	• Weak procurement skills and lack of data: may lead to inadequate or non-existent demand forecasting. • Legal constraints on budget: in some countries, it is mandatory that budgets be done on an annual basis only, preventing the possibility to do multi-year contracts. • *The example of UNICEF*: long-term agreements and reliable long-term forecasting are both part of UNICEF vaccine procurement principles to promote healthy markets and strengthen vaccine supply security. These activities allow manufacturers to confidently make the necessary investments to ensure long term supply and be better prepared to deal with fluctuations in demand.
		Delivery issues	• Supply chain and stock management: for 13% of countries (6 countries) that reported district level stockout in their JRF in 2015, the cause was a breakdown of the distribution system or poor stock management at lower levels of the supply chain.
		Unaffordability	• Lack of access to vaccines at affordable prices: many countries, particularly MICs, have raised this issue at the World Health Assembly (e.g. resolution 68.6 on the GVAP at the 2015 WHA). This is considered a factor that limits access and may prevent demand materialization. It is also difficult to know in advance under which price ceiling a country will deem a vaccine affordable and will consider its introduction.
		Emergencies, outbreaks and surveillance	• Events creating unexpected demand: natural disasters and conflicts are often unpredictable and generate unexpected demand. • Using stockpiles: stockpiling is used to make sure that doses of vaccines are readily available in case of a high increase in demand, for instance during an outbreak. There are international stockpiles (e.g. the International Coordinating Group (ICG) with meningitis, cholera and yellow fever vaccines) and some countries maintain national level stockpiles (e.g. the US Paediatric Vaccine Stockpile Programme maintains a 6-month supply of routine childhood vaccines). For vaccines used both in routine immunisation and in outbreak response, stockpiling may reduce availability of vaccines for routine immunisation. • Global surveillance: surveillance systems can accelerate the response to an outbreak and therefore limit the sudden increase in vaccine demand. However, real-time surveillance is not possible in most systems and quality of currently reported data vary from country to country.
INFORMATION	**Supply information**	Limited global information available on current and future supply capacity and	• Information not easily accessible: information available is not centralised and easy to access. For instance, some manufacturers are now displaying a list of vaccines in short supply on the internet, but information is scattered across several manufacturers' websites. • No strategic planning for global supply: e.g. several countries stopped their local production of BCG because production was not sustainable and prices higher than what was available on the global market. Due to lack of intelligence on global availability of the vaccine, decision makers were probably not informed that the global production of BCG was decreasing

		vaccines at risk of a shortage.	(risk assessments not well documented with global supply information). • Limited intelligence of manufacturing capacity: limited knowledge on current and potential capacity, as well as investments on production capacity and potential to increase portfolio of vaccines produced. • Non-exhaustive information available at the global level: UNICEF has supply information from manufacturers it works with, including for non-Gavi supported vaccines and even some non-PQ products. UNICEF however does not have information on vaccines used in self-procuring countries only (e.g. aP vaccines, HepA, rabies, …). WHO also has only partial data from prequalified manufacturers (from 23 countries).
	Demand information	Limited global information available on demand evolution, particularly for non-Gavi countries	• Limited demand information outside of Gavi supported countries: there is no regular collection of information on how demand is evolving or might evolve in non-Gavi countries as well as for self-financed vaccines in Gavi countries. • Impact of policy & recommendations: no information shared at the global level on new policies and schedule recommendations (e.g. adding a booster dose, new recommendations for maternal immunisation, …) implemented in countries. These changes impact country demand patterns and may therefore disrupt the balance between supply and demand.
	Timely communication	Lack of timely communication between supply and demand, particularly for self-procuring countries	• Translation of policies and strategies into supply needs: lack of early translation of new policies and strategies into precise supply needs can lead to shortages because of the lead-time necessary for industry to scale up production. Lack of anticipation of vaccine calendar evolution. Lack of dialogue with industry to adapt industrial plans. • Communication not conducted in a timely manner in case of a shortage: the information often starts to circulate when the shortage is imminent or already happening, allowing little time for reactive measures to be implemented, both from the country's side and from the manufacturer's side (e.g. country stocks already very low , manufacturer unable to ramp up capacity, …). • Lack of early warning systems: some countries use early warning systems to be informed in advance of an upcoming shortage (e.g. in Norway, legislation mandates that manufacturers notify the Norwegian Medicines Agency about impending drug shortages at least 2 months before they occur). However, many countries do not have these systems and there is no warning system at the international level covering all vaccines (UNICEF SD provides updates and warnings for the vaccines procured by the agency). When a shortage happens, countries do not necessarily know if they are the only ones impacted or if the shortage is widespread. • Allocation of doses during a shortage: lack of clarity on mechanism used by manufacturers to allocate supply in case of a shortage may lead to misunderstanding and distrust (e.g. allocations based on health priorities, contractual clauses, other arrangements, etc.)

Sources: Goldstein 2005 ; Offit 2005 ; M.S. Coleman 2005 & 2006 ; Callender 2006 ; Danzon 2005 & 2011 ; Hitchcock 2007 ; Light 2009 ; Smith 2011; Woodcock 2012 ; Gordon Douglas 2013 ; Congeni 2014 ; Yen 2015 ; Cacciatore 2016 ; BIOTECanada 2010 ; US CDC website; US FDA website; MesVaccins.net ; UNICEF ; V3P database ; WHO ; WHO regional and country consultations 2014-2015 ; MIC task Force ; GVAP Secretariat Report 2015 ; Press articles ; Oanda.com ; discussions with experts ; discussions with Industry representatives.

Annex 2: Actions and scope of work of the European Commission and ECDC

The European Commission, in cooperation with the World Health Organization (WHO), **the European Centre for Disease Prevention and Control (ECDC)** and the **European Medicines Agency (EMA)**, is working with the European Union (EU) Member States in the Health Security Committee (HSC) according to the Decision 1082/2013/EU on serious cross-border threats to health. The Health Security Committee coordinates health-security measures in the EU and has established a solid basis for preparedness activities by enabling EU governments to exchange information and evaluate health events, functioning as a discussion forum that advises health ministers and facilitating coordinated crisis response by EU governments.

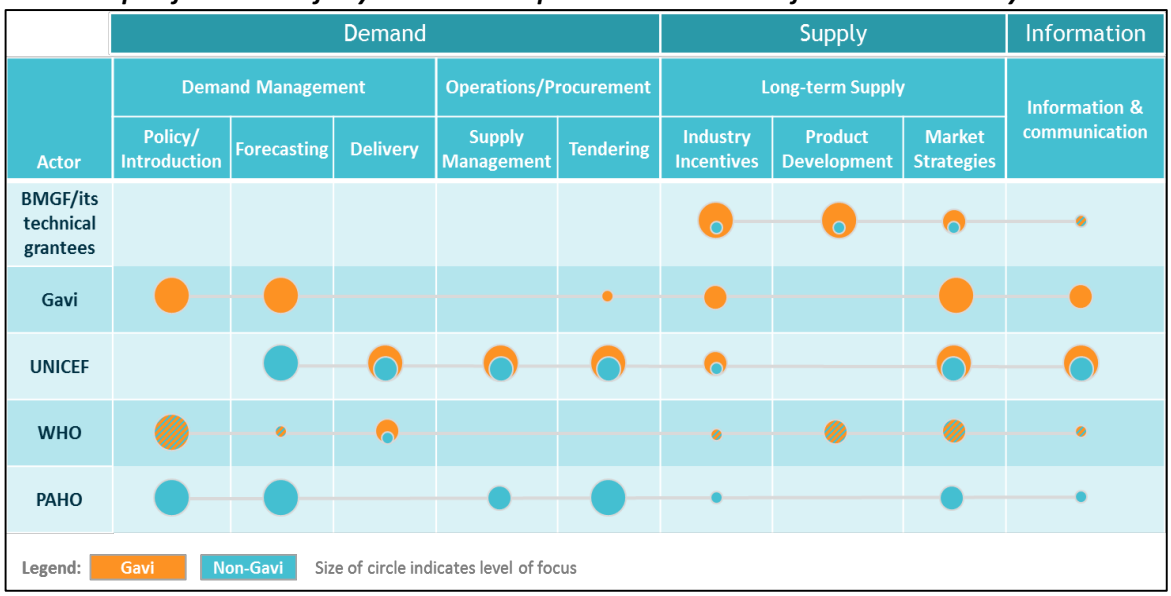
In the European Union vaccination is a competence of the Member States. Council conclusions on vaccination as an effective tool in public health, adopted in December 2014, invite the Member States and the Commission to develop joint action programmes co-financed by the Commission and the Member States to share best practices on national vaccination policies.

In respect to vaccine shortages the Commission, in cooperation with ECDC, EMA and WHO, is working with Member States to identify possible policy interventions in order to address problems related to vaccine supply. Measures proposed are *inter alia* aiming at strengthening mutual assistance of Member States in case of urgent vaccine needs or strengthening vaccine supply infrastructure in Member States, with a view to increase efficiency and reduce expenditures related to vaccine management. As vaccine shortages in the European Union are linked to the situation of the global vaccine market it is important to improve communication and exchange information, with a view to raise awareness about the interdependence of all stakeholders involved.

A shortage affecting acellular pertussis-combination vaccines has been of particular concern in the EU since 2015. This vaccine shortage is believed to be due to reduced production capacities of the acellular pertussis antigen needed for the final vaccine formulation of numerous combination vaccines, increased global demand, and vaccine lots failing to meet the necessary release criteria. This unexpected situation has forced some EU/EEA countries to adjust their vaccination programmes to address the vaccine shortage. ECDC has provided technical assistance to EU/EEA Member States proposing options for possible solutions.

Annex 3: Actions and areas of work of key partners[24]

Landscape of activities of key international partners in the area of vaccine market dynamics:



The Bill & Melinda Gates Foundation (BMGF) focuses on product innovation and developing long-term competition in markets mainly through financial and technical support for manufacturers to help accelerate R&D and WHO prequalification of new vaccines. BMGF works closely with partners to ensure vaccine markets are healthy and serve the needs of low-income countries. BMGF also coordinates with the Gavi Secretariat to gather market intelligence and insights on the state of different markets and to develop appropriate market incentives to meet objectives identified in product roadmaps. Much of this work is achieved by funding other global health partners (CHAI, PATH, AMP, JSI, JHSPH, etc.) to leverage their specific technical expertise.

The Gavi Secretariat coordinates the participation and contribution of key Alliance members, leads in the development and implementation of the product market strategy (or ' supply and procurement roadmap') and monitors progress against indicators in the Alliance Supply and Procurement Strategy. The Secretariat shares available non-confidential vaccine market information. Importantly, the Secretariat produces vaccine-specific strategic demand forecasts and shares these within the Alliance, including with manufacturers. As part of product roadmap development, the Secretariat convenes consultations with technical Alliance members, additional disease/vaccine experts, and other global health organisations with relevant expertise. The Secretariat also engages with manufacturers; coordinates with UNICEF to ensure procurement decision-making aligns with roadmap objectives; and supports WHO to develop product standards and specifications. The scope of Gavi's market shaping activities covers all countries receiving Gavi support. Gavi is committed to support governments to transition successfully towards self-financing. This includes efforts to strengthen national capacity in vaccine procurement, financing and regulation during the transition process.

The United Nations Children's Emergency Fund (UNICEF) works for a world in which every child has a fair chance in life. In 2014, UNICEF procured $3.38 billion worth of supplies and services from all over the world (including $1.48 billion in vaccines) in support of programmes to help children survive

[24] Note that this is a working document that is still under development and review.

and thrive throughout the world. Through fair and open procurement, UNICEF influences markets to ensure a diverse and reliable supplier base, a competitive landscape, and affordable and quality products in the right formulations for children. UNICEF is responsible for buying all vaccines and related items for global campaigns to eradicate polio, eliminate neonatal and maternal tetanus, and control measles. In addition, UNICEF procures vaccines for its own programmes and for Gavi. UNICEF's procurement and market influencing efforts are built on an in-depth understanding of market forces, accurate forecasting and analysis, transparency, engagement with industry, collaboration with key partners, and a drive for the best possible outcome for children.

The World Health Organization (WHO) works with partners on demand, supply and information aspects to support short term access and long term strategies aiming at strengthening healthy markets. On the supply side, WHO provides R&D support, establishes guidelines (e.g. guidelines on GMP for biological products revised in October 2015), provides technical assistance to countries (e.g. facilitating technology transfer to 14 developing countries on influenza vaccine since 2006), supports National Regulatory Authorities (NRAs) of producing countries (36 out of 44 have been assessed as functional) and manages the well-established prequalification process to ensure availability of products of assured quality (in 2015, there were more than 140 prequalified vaccines from 32 manufacturers, a 5-fold increase since 2001). Fast-tracking procedure for prequalification is also a measure to increase the supply base in a short amount of time (e.g. Green Signal BCG vaccine prequalified in February 2016). Finally, WHO explores needs and opportunities for regional vaccine production (e.g. in Africa).
On the demand side, WHO works in collaboration with partners to expand timely access to vaccines in all countries through supporting decision making processes (NITAG, cost effectiveness analyses, position papers, policies and recommendations), strengthening political commitment and financing (work with country to analyse financial needs and trends, CMYP and JRF), reducing vaccine hesitancy, collaborating with UNICEF to strengthen country procurement capabilities, strengthening NRAs and simplifying country product registration requirements (including for fast track registration). In 2015, WHO and partners developed the MIC strategy to specifically address issues that Middle Income Countries (MICs) face to raise coverage and enable new vaccine introductions. Nevertheless, it should be noted that available resources for this work are limited and unpredictable, preventing more systematic and comprehensive efforts.

The Pan American Health Organisation (PAHO) is a specialized health agency of the Inter-American System
and serves as WHO's Regional Office for the Americas. PAHO provides technical cooperation and mobilizes partnerships to improve health and quality of life in the countries of the Americas. PAHO's Revolving Fund for Vaccine Procurement has provided crucial support for the region's achievements, including its elimination of vaccine-preventable diseases and its introduction of new vaccines, such as rotavirus, pneumococcal disease, and HPV. Between June 2014 and June 2015, the fund procured more than US$ 547 million worth of vaccines and US$ 3.5 million worth of syringes for immunisation programmes in 41 participating countries and territories. The Revolving Fund has become an example for other international organizations and other WHO regions of an effective mechanism to ensure an uninterrupted supply of affordable, quality vaccines in the complex global vaccine market. Increasing Member States' awareness of global vaccine market dynamics and challenges, support for demand planning, and ensuring the timely availability of quality vaccines and supplies are key elements of PAHO's technical cooperation.

World Health Organization

EXECUTIVE BOARD
138th session
Provisional agenda item 10.5

EB138/41
18 December 2015

Addressing the global shortages of medicines, and the safety and accessibility of children's medication

Report by the Secretariat

1. In recent years, shortages of essential medicines have been documented in most parts of the world with increasing frequency. The common denominator for these shortages is that medicines likely to be in short supply are products that are mostly old, off-patent or difficult to formulate and that have a tightly-defined shelf life and few or a sole manufacturer.[1] Injectable products are particularly at risk. The reasons for shortages have been investigated in many studies and in several countries, and the leading possible causes include: difficulties in acquiring raw materials, manufacturing problems, barriers to competition, business decisions, the impact of new technologies, expensive medicines, and fragmented markets.

2. These reasons combine with characteristics of supply systems to worsen any interruption in manufacturing. Notably, there is poor availability and quality of data on actual demand; inadequate management practices in procurement and the supply chain, combined with large tender contracts that do not sufficiently define quality standards but whose sole emphasis is on obtaining the lowest prices; and too small profit margins for manufacturers – all these factors may lead to shortages. Benzathine penicillin, for example, has been in chronic short supply for several years because of problems with manaufacturing and thus the quality of the product, lack of consistent demand, and a decrease in indications for its use and a relatively low price.[2]

3. Medicines for children are also subject to shortages. Many regulatory authorities have limited capacity to undertake appropriate regulation to ensure good-quality products for children, clinical trials are not always done in paediatric populations, and there are problems with the capacity to diagnose uncommon diseases in children. Examples are endocrine disorders in children, which can be treated very effectively – when they are recognized – with a small group of essential medicines that are mostly off-patent but seem to be in short supply globally.

[1] Gehrett BK. A prescription for drug shortages. Journal of the American Medical Association 2012;307:153–154. doi:10.1001/jama.2011.2000.

[2] Wyber R, Taubert K, Marko S, Kaplan EL. Benzathine penicillin G for the management of RHD: concerns about quality and access, and opportunities for intervention and improvement. Global Heart 2013:8;227–234 DOI: http://dx.doi.org/10.1016/j.gheart.2013.08.011 (accessed 7 December 2015).

CONSEQUENCES OF SHORTAGES

4. Negative impacts of shortages are inability to fulfil prescriptions as well as poor quality prescribing and poor use of medicines. The results are poor health outcomes, which have been documented, for example, in relation to mortality in children owing to lack of cancer treatment and to inappropriate use of antibiotics when first-line regimens are not available. Inappropriate use of second- and third-line regimens can contribute to drug resistance, limit treatment options and often have higher cost. The global burden of undertreatment and failure to treat is not known; however, the problem of shortages, given their increasing trend, combined with poor use of medicines will become increasingly complex to resolve. Where shortages have been experienced, there have been reports of spurious/falsely labelled/falsified/counterfeit medical products entering the supply chain, with risks for the health of patients.

5. High-income, middle-income and low-income countries all may have different reasons for shortages in relation to supply chains, but payment systems for products can cause problems in all settings. Changes in payment structures or systems that provide perverse incentives to use expensive products may also lead to shortages of low-priced alternative treatments. Rigid, lengthy or inadequate tender processes may also contribute to the problem and, although there may be strategies to limit the risk of supply through sole tenders (for instance, penalties for failure to supply), research is needed on how effective these have been in reducing shortages in different settings.

COUNTRY APPROACHES TO LIMIT SHORTAGES

6. Several strategies have been tried to avert or reduce shortages. Multiple reporting systems exist within specialized programmes or at national level in high-income countries. For example, manufacturers in European Union member states are obliged to inform the health authorities in advance of possible future shortages. A combination of notification systems and systematic regulatory and reimbursement responses may help at a health-system level, together with a systematic approach to the clinical use of products in short supply. It is not clear yet whether mandatory or voluntary notification works best and who should do the notifying – let alone considerations on whether these processes can be applied in countries with weak regulation and information systems.

7. Additional approaches to managing acute shortages, preventing future shortages and reducing the impact of shortages on the provision of care to patients include: the use of online information systems to facilitate direct reporting to health authorities of information on shortages; coordination between producers; and, in some situations, the use of exceptional procedures for the granting of market authorizations. Also, some countries have promoted initiatives to encourage the production and registration of generic versions of medicines in short supply.

8. Mechanisms for combining and sharing notifications for global scrutiny of the status of the supply of individual medicines could be investigated and explored. As the supply of pharmaceuticals is a multinational business, having a system for comprehensive evaluation and a future global monitoring mechanism for that supply in place, would anticipate and detect early shortages and assist the development of a joint rapid response mechanism to encourage countries, the international community and other relevant stakeholders to cooperate in developing a joint rapid response.

9. Pricing interventions can also be used to reduce shortages. In the Australian context, manufacturers can request a higher price for products with limited markets.[1] It has been suggested that in the context of the United States of America, where prices of oncology products decreased following the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, that setting minimum prices for some products in order to encourage continuity of supply would improve supply of oncology products.

10. It is important to develop proactive strategies with actions to be taken to identify and maintain the supply of medicines that are essential for health care and that are vulnerable to shortages in supply. The usual market approach to medicines supply through encouraging generic manufacturers to produce the medicines of interest has shown enormous benefits in lowering prices and increasing affordability. Too low prices, however, may drive manufacturers out of the market, and higher prices of alternative newer products may result in them being preferentially supplied, with a decline in market for vital but cheaper medicines. Limiting competition can also result in problems with supply.

NEW STRATEGIES TO MITIGATE THE RISK OF SHORTAGES

11. At the global level, a set of essential medicines could be identified for which shortages have been reported or there exists a risk of shortages, and an international agreement about ensuring continuity of manufacturing and supply could be investigated. For example, successful treatment of many oncological and immunological conditions without methotrexate is severely jeopardized – yet this product has been reported as in short supply repeatedly. Questions that a general international agreement would have to resolve include: could a multi-year global advance purchase commitment be worked out? Would an agreed global minimum price that is commercially attractive help to keep a medicine on the market? How would such a price be set?

MEDICINES FOR CHILDREN

12. The adoption by the Health Assembly in 2007 of resolution WHA60.20 on better medicines for children led the Secretariat to introduce a programme of work on that subject. Its results have included creation of the WHO Model List of Essential Medicines for Children (most recently updated in April 2015), the setting of global standards for formulations of medicines for children, identification of clinical trials in children through the WHO International Clinical Trials Registry Platform, publication of information about prices of selected medicines for children, and identification of missing products, such as fixed-dose combination medicines containing the appropriate dose of the components for tuberculosis in children.

13. The shortage of treatments of tuberculosis for children was successfully addressed by WHO and its partners. After a change in tuberculosis treatment guidelines in 2010, the pharmaceutical industry was reluctant to invest in redeveloping medicines to treat children with tuberculosis, citing the cost of new trials for regulatory submissions and the fact that the market was small and poorly understood as barriers to investing. UNITAID's STEP TB Project invested in trials to reduce risk and engaged with manufacturers to ensure regulatory submissions. The Project also worked with countries with high

[1] See Australian Government Department of Health, The Pharmaceuticals Benefit Scheme, http://www.pbs.gov.au/info/industry/pricing/pbs-items/fact-sheet-requesting-a-change-to-an-existing-price (accessed 7 December 2015).

burdens of tuberculosis and major procurers to improve the ability to quantify the actual demand and need.

14. Shortages of each product (or group of similar products) will have different causes and their rectification will require specific and targeted interventions. Other products for children are also listed on the invitations for expression of interest issued by the WHO Prequalification Programme for HIV/AIDS, including hepatitis B and C, and malaria, and interventions continue with the aim of securing their availability, from manufacturing to national supply chains.

15. The Paediatric medicines Regulators Network was established to promote collaboration between regulatory authorities on the regulation of medicines for children. Some high-income countries have legislation related to medicines for children with the aim of optimizing and promoting the development of appropriate products, but similar legislation is not generally in place in low- and middle-income countries. There will be value in further developing the Network and providing more support to countries for building appropriate capacity to regulate medicines for children appropriately and encourage their research and development.

16. Prices of paediatric medicines are generally higher than equivalent products for adults. In part, this price differential may be due to higher development costs of special dosage forms for children and the need for additional clinical trials. A better understanding of research and development costs would enable a constructive dialogue on how to establish a fair and affordable price for medicines for children.

17. Understanding the costs of development of medicines is particularly important for uncommon and genetic diseases in children (variously classified as orphan and rare diseases). New and effective products for many genetic disorders are becoming available but they are generally extremely expensive. Further there is a degree of confusion between what are truly orphan or rare diseases, based on the global burden of disease, and what have been defined as orphan diseases for the purposes of regulatory authorities who can provide incentives for manufacturers to encourage their development and production. There is some evidence that these incentives are now being exploited, resulting in high prices and problems with access. Should a country choose to make these products available through health insurance schemes, the impact on their pharmaceutical budgets can be substantial.

18. Overall, the demand side of the market for many medicines may need to be more actively managed. There are limited data to guide manufacturing and procurement decisions about medicines for many diseases in children. At the same time, health care workers try to provide effective care through the use of extemporaneous preparations, which may offer short-term solutions but may also be associated with risks due to poor quality production. Health care workers may also have limited expectations and confidence in the availability and value of medicines for children and hence not promote their use.

TOWARD A POTENTIAL SYSTEMIC APPROACH TO PREVENT AND MANAGE SHORTAGES OF ESSENTIAL MEDICINES

19. Several options exist for actions that may lead to a reduction of the problem of shortages, both generally and specifically for medicines for children. These options include:

(a) application of a globalized notification system and response mechanisms;

(b) proper assessment to define products at risk;

(c) global agreement on actions to diminish specific shortages;

(d) expansion of regulatory collaboration on essential medicines susceptible to shortages;

(e) centralized negotiation to preserve essential medicines susceptible to shortages including definition of minimum volume and fair price;

(f) analysis and understanding of costs of research and development for medicines for uncommon diseases in children;

(g) expand the activities of the Paediatric medicines Regulators Network to promote appropriate legislation, regulatory strategies and capacity, and monitoring of medicines in children;

(h) continue to promote ethical and appropriate clinical trials in children of all age groups;

(i) work with partners to ensure appropriate demand for medicines for children, including medicines for uncommon diseases.

20. Meeting the targets specified in relation to access to medicines in Sustainable Development Goal 3 (Ensure healthy lives and promote well-being for all at all ages), as well as completing the unfinished agenda of the Millennium Development Goals, will require coordinated action to address the factors described in this report. Continuing to react to stockouts on a case-by-case basis, especially those caused by market dynamics, will severely compromise the ability to achieve equitable access to essential medicines; more active approaches to shaping the market for essential medicines on a global scale will be needed.

ACTION BY THE EXECUTIVE BOARD

21. The Board is invited to note the report.

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RAPID RISK ASSESSMENT

Shortage of acellular pertussis-containing vaccines and impact on immunisation programmes in the EU/EEA (first update)

2 February 2016

Main conclusions and options for response

The vaccine shortage currently affecting some EU/EEA Member States has already had direct consequences for the delivery of national vaccination programmes.

In general, the supply situation appears similar to what was previously reported, and uncertainty prevails. Some countries had to make short-term arrangements with other countries to avoid interruption of their programmes.

Since 2015, nine EU/EEA Member States have adjusted their immunisation policies. Measures included the following:

- Temporary suspension of the primary immunisation scheme
- Temporary suspension of the booster at pre-school age
- Changes to the primary immunisation schedule with regard to age at which the vaccine is given
- Modification of the vaccine formulation used as a pre-school booster
- Delayed introduction of a new antigen into the primary immunisation scheme
- Prioritisation of vaccine formulation for the primary immunisation scheme
- Use of acellular pertussis-containing vaccines not authorised in the EU

Should shortages persist at the national level, several options should be considered. These options are listed below and have been updated since the previous RRA on acellular pertussis-containing vaccines.

As much as possible, the primary immunisation schedule should be preserved in order to ensure the early and adequate protection of newborns. If alternative vaccines or other vaccine presentations are available, their use should be prioritised, in conjunction with appropriate monitoring of safety and effectiveness, rather than modifying the vaccination schedule. Preference should be given to the use of combination vaccines with the highest number of antigens.

Priority should be given in the following order:

- The infant primary immunisation series (first year of life)
- The first toddler booster (second year of life) dose
- If applicable, the first toddler booster dose should be prioritised over the school-entry booster.

Suggested citation: European Centre for Disease Prevention and Control. Shortage of acellular pertussis-containing vaccines and impact on immunisation programmes in the EU/EEA – 2 February 2016. Stockholm: ECDC; 2016.

In countries where vaccination during pregnancy is recommended, and if Tdap vaccine is in short supply, it is suggested that doses should be preserved for maternal immunisation, instead of adolescent or pre-school booster doses, as maternal immunisation directly benefits newborns.

More evidence on the level of protection offered by the following strategies is needed:

- Use of a low-antigen-content pertussis vaccine as pre-school booster instead of a regular-dose vaccine, and vaccination of these cohorts at a later age.
- Maternal immunisation blunting the responses to some vaccines in the infant immunisation schedule.

Source and date of request

Directorate General for Health and Food Safety (DG SANTE), 25 January 2016

Public health issue

Early in 2015, a shortage of acellular pertussis-containing combination vaccines for use in the EU/EEA immunisation programmes was brought to the attention of ECDC. This was addressed in a previous RRA published in October 2015 [1].

This RRA focuses on acellular pertussis-containing combination vaccines used in national vaccination programmes in the EU/EEA Member States (see Table 1).

Its objectives are:

- to provide an overview of the situation in the EU/EEA Member States and changes made to the routine vaccine schedules in order to overcome shortages;
- to provide updated options to be considered by EU/EEA Member States in order to adjust their national vaccination schedules to overcome supply challenges.

This rapid risk assessment is not intended:

- to propose a universal EU vaccination schedule that can completely accommodate all national situations;
- to provide an extensive evidence-based review of options on how to modify vaccination schedules;
- to discuss specifics of the various combination vaccines available on the EU market, i.e. number and types of aP vaccine components, antigen concentration of the individual vaccines or the role of combined or concomitantly administered vaccines*;
- to address vaccine procurement processes at the national level.

Consulted experts

ECDC experts (in alphabetical order): Tarik Derrough, Lucia Pastore-Celentano

The following external experts contributed to this risk assessment:

Nicole Guiso, Institut Pasteur, Paris, and Marta Granström, Karolinska Institute, Stockholm

ECDC acknowledges the valuable contributions of all experts. The experts have submitted declarations of interests that were reviewed by ECDC and found not to be in conflict with the comments and suggestions made. The opinions expressed by individual experts do not necessarily represent the opinions of their institutions.

Abbreviations

aP: Acellular-pertussis (full-dose content)

ap: Acellular pertussis (low-dose content)

wP: Whole-cell pertussis

T: Tetanus antigen

D: Diphtheria antigen

d: Diphtheria antigen (reduced dose)

* It is understood that the use and type of vaccines should be in accordance with national vaccination policies and the summary of product characteristics of each vaccine.

DT: Diphtheria and tetanus antigens combination vaccine

DTaP-IPV: Combination vaccines that contain diphtheria (full dose), tetanus, acellular pertussis (full dose) and inactivated poliomyelitis antigens. Also referred to as 'tetravalent' vaccine.

DTaP-IPV/Hib: Combination vaccines that contain diphtheria (full dose), tetanus, acellular pertussis (full dose), inactivated poliomyelitis antigens and Hib antigen (to be reconstituted for some vaccine presentations). Also referred to as 'pentavalent' vaccine.

DTaP-IPV-Hib-HepB: Combination vaccines that contain diphtheria (full dose), tetanus, acellular pertussis (full dose) inactivated poliomyelitis antigens, Hib and Hepatitis B antigens. Also referred to as 'hexavalent' vaccine.

DTwP: Combination vaccines that contain diphtheria (full dose), tetanus and whole-cell pertussis antigens.

Tdap: Combination vaccines that contain tetanus, diphtheria (reduced dose content) and acellular pertussis (low antigen content).

Tdap-IPV: Combination vaccines that contain tetanus, diphtheria (reduced dose content), acellular pertussis (low antigen content) and inactivated poliomyelitis antigens.

Hib: *Haemophilus influenzae* type b

'2p+1' schedule: Primary immunisation schedule corresponding to two doses of primary vaccination and a booster dose, usually all given within the first 12 months of life and starting as early as at two months of life.

'3p+1' schedule: Primary immunisation schedule corresponding to three doses, given in the first year of life, starting as early as at two months of life, with a booster in the second year of life.

Background

Vaccine shortage is believed to be due to reduced production capacities for the acellular pertussis antigen that enters the final vaccine formulation of numerous combination vaccines, increased global demand for those combination vaccines that are also used throughout the EU/EEA Member States, and vaccine lots failing to meet the necessary release criteria.

This shortage forced some EU/EEA countries to adjust their childhood vaccination programmes in order to address the vaccine shortage. In some cases ad-hoc measures to procure vaccines were implemented.

Pertussis vaccines do not exist as stand-alone vaccines. Therefore, the current shortage affecting the acellular pertussis component not only negatively impacts pertussis protection but also poses the risk of reduced availability of combination vaccines containing an acellular pertussis component, in particular those that also protect against tetanus, diphtheria, polio and invasive bacterial disease caused by Hib.

These diseases are severe, and any failure to provide a high level of vaccination coverage can have dramatic consequences. For example, Ukraine reported two paralytic cases of poliomyelitis in August 2015 related to a vaccine-derived poliovirus strain in combination with low vaccination coverage [3].

Event background

In early 2015, a limited supply of combined vaccines for primary immunisation and booster series was brought to the attention of the ECDC.

Several EU/EEA Member States have requested technical assistance from ECDC, which lead to an information exchange between ECDC and EU/EEA Member States through the epidemic intelligence information services platform for vaccine-preventable diseases (EPIS-VPD) as well as during a Health Security Committee (HSC) teleconference in April 2015. Several countries reported that they had a limited stockpile of vaccines for use in their routine programmes and that it was difficult to procure specific vaccine combinations.

On 23 September 2015, the ongoing supply issues – alongside possible increased demand to vaccinate newly arrived migrants – were discussed during an HSC teleconference.

On 8 October 2015, ECDC published an RRA.

In January 2016, ECDC asked its National Focal Points for an update on the supply situation for acellular pertussis-containing combination vaccines and for information on the adjustments made to national immunisation programmes to overcome the shortage (Annex 1, Table 1).

Since 2015, nine EU/EEA Member States have adjusted their immunisation policy. Measures included the following:

- Temporary suspension of the primary immunisation scheme (e.g. Bulgaria)
- Temporary suspension of the booster at pre-school age (e.g. Bulgaria , Spain)
- Changes to the primary immunisation schedule with respect to age of vaccine administration in order to save doses (e.g. Romania)
- Modification of the vaccine formulation used as a pre-school booster with reduced diphtheria and pertussis

antigen content vaccines (e.g. Belgium, France, Greece, Luxembourg)
- Delayed introduction of a new antigen into the primary immunisation scheme (e.g. Norway)
- Prioritisation of vaccine formulation for the primary immunisation scheme rather than for booster doses (e.g. Spain, Sweden)
- Procurement of vaccines for the primary immunisation scheme from outside the EU (e.g. Romania, Bulgaria)

ECDC threat assessment for the EU

The shortage of acellular-pertussis combination vaccines affecting the EU/EEA Member States is still ongoing and represents a public health threat to the EU. The risk lies in leaving cohorts of children temporarily unvaccinated, or vaccinated with a vaccine formulation that is not recommended for their age group to ensure full protection.

To date, there is no indication on how long this shortage will last, and the situation remains of concern. The negative consequences on vaccination programmes will increase until supplies resume to normal. In the meantime, countries face the growing accumulation of susceptible cohorts and cohorts with suboptimal protection that are at risk of disease. Some countries, such as Bulgaria, are reported to have faced shortages since 2014. Some children did not receive appropriate pre-school vaccination and are in need of catch-up vaccination.

In addition to the potential impact on public health, vaccine shortages also have operational and technical consequences for the delivery and assessment of national immunisation policies and for disease surveillance systems. There are both operational and technical consequences:

Operational consequences

- Need to communicate regularly with public and healthcare professionals with regard to vaccine shortage and adaptation of vaccination schedules in order to avoid confusion.
- Need to ensure adequate documentation of individual vaccinations in order to provide supplementary immunisation to those children that were inadequately vaccinated – once supplies have reached normal levels.

Technical consequences

- Need for enhanced surveillance for selected vaccine-preventable diseases.
- Need to consider the implementation of sentinel hospital surveillance of severe pertussis in young children
- Need to consider improving diagnostic capacities.
- A periodical assessment of the level of protection through regular sero-surveys in cohorts of children who were vaccinated with modified schedules/products may be required.
- Need to enhance the monitoring of vaccine coverage of the cohorts vaccinated with a modified schedule.
- A periodical assessment of the safety profile of the vaccine products used to respond to the shortage may be required.

Options for response

The options presented in the previous RRA remain valid and have been further specified below – in particular on the use of low dose diphtheria and pertussis-combination vaccines not licensed for use in primary immunisation series [1].

The general principle remains, whenever possible, to:

- substitute the missing doses with an alternative combination/formulation vaccine rather than modifying the schedule;
- prioritise strategies that have demonstrated direct benefit towards infants (e.g. primary and maternal immunisation); vaccinating those who have close contacts with infants too young to be vaccinated provides indirect protective effects.

Options for adjusting the primary immunisation series

The priority is to preserve the primary immunisation series, with a minimum of three doses administered by the first birthday.

In case of severe shortages, the following options are suggested (in order of priority):

Interchangeability of vaccines

- If alternative vaccines or other vaccine presentations are available (see below), prioritise their use rather than modifying the schedule (e.g. rather than switching from a '3p+1' to a '2p+1' schedule with the same product) and ensure appropriate monitoring of safety and effectiveness.
- If a hexavalent vaccine (DTaP-IPV-HepB-Hib) is not available for any dose of the infant/toddler series, using the following vaccines could be considered:
  - A pentavalent vaccine (DTaP-IPV/Hib), co-administered with a HepB standalone vaccine
  - A tetravalent vaccine (DTaP-IPV), co-administered with Hib and HepB standalone vaccines
  - A trivalent vaccine (DTaP), co-administered with the recommended standalone vaccines.
- If a pentavalent vaccine (DTaP-IPV/Hib) is not available for any dose of the infant/toddler series, using the following vaccines could be considered:
  - A hexavalent vaccine according to indication (even if there is no recommendation to routinely vaccinate against HepB) as the priority remains the protection against Hib and pertussis in infants, or
  - A tetravalent vaccine (DTaP-IPV), co-administered with a Hib standalone vaccine, or
  - A trivalent vaccine (DTaP), co-administered with the recommended standalone vaccines.

Modification of the age at administration

In countries with a '3p+1' schedule, one of the primary doses in the first year of life could be temporarily suspended. The primary booster dose would then be moved up and offered at around the time of the first birthday [8]. This would correspond to the first booster dose of a '2p+1' schedule, with a two-month interval between doses. Supplementary school-entry booster vaccinations should be considered for these cohorts of children, in accordance with national vaccination policies.

Use of low dose diphtheria and pertussis-combination vaccines not licensed for use in primary immunisation series

Combination vaccines licensed in the EU/EEA Member States that contain a low-dose pertussis and diphtheria antigen (e.g. Tdap; Tdap-IPV) are not licensed for use in primary immunisation schedules. They do not contain a Hib or HepB antigen, which would have to be provided alternatively whenever needed in the schedule.

This category of vaccines has not undergone clinical trials in the age groups targeted in the primary series and, to our knowledge, there is no published information on their unlicensed usage. The earliest age at which these vaccines could be used is three years, but this may vary according to the commercial product.

It is acknowledged that the pertussis and diphtheria concentration of the antigens are considered as insufficient to prime infants and trigger an immune response that provides clinical protection. Their use should only be considered as a last option if no alternative exists for the primary vaccination so that infants will not remain unvaccinated. In this scenario, available vaccines should be used with a pertussis toxoid (PT) antigen content as close to 25 µg as possible (as in vaccines used for primary immunisation).

A careful assessment of the situation should be conducted prior to implementation. Effectiveness should be monitored through serological and clinical surveillance. It is advised:

- to perform serological surveillance by measuring diphtheria-neutralising antibodies according to the recommended in vitro methods [9] in a reference laboratory able to measure neutralising antibodies against diphtheria. Circulating diphtheria antitoxin levels in individual serum samples above the threshold of 0.1 IU/ml are indicative of full protection against diphtheria. Diphtheria serology is suggested in the light of the absence of established immunological correlates of protection for pertussis [6];
- to ensure the documentation of individual vaccinations in order to provide supplementary immunisation when supplies have returned to normal levels. It is advised to then administer DTaP-containing vaccine before the children reach school age.

Options for possible adjustments to the pre-school, adolescent and adult immunisation series (from three years of age)

Interchangeability of vaccines

For the school-entry booster, if a tetravalent vaccine (DTaP-IPV) product is not available, the following options could be considered:

- Use of a Tdap-IPV vaccine (or TdaP and IPV vaccines co-administered) [10,11], as adopted by Belgium, France and Greece as a temporary measures (Table 1).
- Alternatively, use of a Td-IPV vaccine or the co-administration of Td and IPV vaccines. In this case, however, no vaccination against pertussis would be offered.
- Delaying the administration of the booster dose until the supply of pertussis-containing combination vaccine has returned to normal levels.

Options for vaccination during pregnancy

In countries where vaccination during pregnancy is recommended, and if a Tdap vaccine is in short supply, it is suggested that doses for maternal immunisation should be preserved over adolescent or pre-school booster doses, as maternal immunisation directly benefits newborns. Similarly, pre-school and adolescent booster doses should be prioritised over adult booster doses.

This can be schematically summarised as follows in terms of the order of preference, should severe shortages occur at the country level and prioritisation be needed. The symbol '>' suggests that the preceding population group is a preferred target for vaccination, whenever applicable:

Maternal > Pre-school booster > Adolescent booster > Adult booster

In countries where vaccination in pregnancy is not recommended, its implementation could be considered as a means to protect unvaccinated infants affected by shortages [12].

Conclusions

The vaccine shortage currently affecting some EU/EEA Member States has already had direct consequences for the delivery of national vaccination programmes. Since 2015, nine EU/EEA Member States had to adjust their immunisation policies.

In general, the supply situation appears similar to what was previously reported, and uncertainty prevails. Some countries had to make short-term arrangements with other countries to avoid interruption of their programmes.

Should shortages persist at the national level, several options should be considered. These options have been updated since the previous RRA on acellular pertussis-containing vaccines.

The primary immunisation schedule should be preserved as much as possible in order to ensure the early and adequate protection of newborns. If alternative vaccines or other vaccine presentations are available, their use should be prioritised, in conjunction with appropriate monitoring of safety and effectiveness, rather than modifying the vaccination schedule. Preference should be given to the use of combination vaccines with the highest number of antigens.

Priority should be given in the following order:

- The infant primary immunisation series (first year of life)
- The first toddler booster (second year of life) dose
- If applicable, the first toddler booster dose should be prioritised over the school-entry booster.

In countries where vaccination during pregnancy is recommended, and if Tdap vaccine is in short supply, it is suggested that doses should be preserved for maternal immunisation, instead of adolescent or pre-school booster doses, as maternal immunisation directly benefits newborns.

More evidence on the level of protection offered by the following strategies is needed:

- Use of a low-antigen-content pertussis vaccine as pre-school booster instead of a regular-dose vaccine, and vaccination of these cohorts at a later age.
- Maternal immunisation blunting the responses to some vaccines in the infant immunisation schedule.

Annex 1. Overview table

Table 1. Shortage of aP-containing vaccines in EU/EEA Member States and impact on vaccination policy, as of 28 January 2016

Country	Situation update as of	Source	Current or anticipated shortages	Impact on vaccination policy and mitigation		Comments	Impact (January 2016)
				Primary immunisation	Booster doses		
Austria	26 Jan 2016	Communication to ECDC	**Current**: Shortage of dTaP-IPV combination vaccines for booster doses on the private market in 2014 and 2015.	**None**	**Limited:** In some cases, delay of booster doses for school children in the free national immunisation programme. Delay of booster doses for adolescents and adults who are vaccinated with vaccines from the private market.	The situation is expected to improve in 2016	
Belgium	26 Jan 2016	Communication to ECDC; official statement*	**Current**: aP combination vaccines – DTaP-IPV	**None**	**High**: Pre-school booster affected. DTaP-IPV and temporary replacement by Tdap-IPV (same manufacturer but lower dose of diphtheria/tetanus/pertussis antigens)		
Bulgaria	26 Jan 2016	Communication to ECDC	**Current:** Shortage of aP combination vaccines: hexa-, penta- and tetravalent. No tenders for hexa- and pentavalent vaccines are opened. In January 2016, a tender procedure for tetravalent vaccines for boosters for 2015 was initiated.	**Very high**: In 2015, primary immunisations were affected by penta- and hexavalent vaccine shortages. Immunisation gaps were partially closed by donation of pentavalent vaccines from Turkey in July and at the end of the year.	**Very high**: In 2015, the administration of the pre-school booster with tetravalent vaccine was suspended. At the end of 2015, smaller quantities of tetravalent vaccines could be bought, which were used primarily for booster immunisations in children who missed the pre-school vaccination in 2014.		
Croatia	25 Sep 2015	Communication to ECDC	**Current:** Td vaccine used for adult booster **Expected:** aP combination vaccine (hexavalent, DTaP, Tdap)	**Limited:** Introduction of hexavalent vaccination connected to, but not dictated by, shortage in pentavalent vaccine	**None**		
Czech Republic	26 Jan 2016	Communication to ECDC	**Current:** DTaP (used as a booster dose at 5–6 years; the proposal is to replace it with DTaP-IPV. Repeated interruptions in the supply of Tdap vaccine for adults.	**None**	**None**		
Cyprus							
Denmark	26 Jan 2016	Communication to ECDC	**Current:** dTap-IPV (SSI product) for booster vaccination at five years of age. DTaP-IPV/Hib (SSI product) for primary vaccination	**Limited**: SSI product will be replaced by other hexavalent vaccines†.	**None**		

* http://www.provac.org/pdf/TETRAVAC_Repevax-FAQ_Provac_sept2015.pdf

† http://www.ssi.dk/Aktuelt/Nyhedsbreve/EPI-NYT/2016/Uge%203%20-%202016.aspx

Country	Situation update as of	Source	Current or anticipated shortages	Impact on vaccination policy and mitigation		Comments	Impact (January 2016)
				Primary immunisation	Booster doses		
Estonia	26 Jan. 2016		No shortage but limited stocks for BCG	**None**	**None**		
France	25 Feb 2015	Official statement*	Shortage of combination vaccine with lower pertussis antigen content (aP-combo family). Impact on pre-school booster. Decision to introduce Tdap-IPV at six years of age instead of DTaP-IPV combination vaccine	**None**	**High**: Pre-school booster affected. DTaP-IPV temporary replaced by Tdap-IPV and DTaP-IPV recommended for the booster for 11–13-year-olds of the cohort currently affected.		
Finland	26 Jan. 2016	Communication to ECDC	No shortage but limited stocks for DTaP	**None**	**None**		
Germany	26 Jan 2016	Communication to ECDC; official statement†	**Current:** aP combination vaccines – DTaP-IPV/Hib. Shortage of single products. Products can, however, be replaced by others that are still available on the market.	**None**	**None**		
Greece	26 Jan 2016	Official statement (15 October 2015)‡	**Current:** shortage of tetravalent (dTap-IPV) and pentavalent vaccines	**None**	**High**: Temporary replacement of pentavalent second-year-of-life booster dose by hexavalent vaccine. Temporary replacement of pre-school DTaP-IPV booster by Tdap-IPV or temporary delay of administration.		
Hungary	26 Jan. 2016	Communication to ECDC; official statement‡	**Current:** No shortage in DTaP-IPV-Hib combined vaccine.	**None** From 1 April 2016, switch from a 2, 4, 6 schedule with booster dose at 21 months to a 2, 3, 4 months schedule with a booster dose at 18 months.	**None**		
Iceland	26 Jan 2016	Communication to ECDC	**None**	**None**	**none**		
Ireland	26 Jan 2016	Communication to ECDC	**None**	**None**	**None**		
Italy	26 Jan 2016	Communication to ECDC; official statement§	**Current:** Shortages in Tdap, DTaP-IPV and DTaP-IPV-Hib	**None** because hexavalent vaccine is used for primary immunisation	**None**		
Latvia	26 Jan. 2016	Communication to ECDC	**None**	**None**	**None**		

* http://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=480

† http://www.rki.de/DE/Content/Kommissionen/STIKO/Lieferengpaesse/Lieferengpaesse_node.html

‡ http://www.hgye.hu/hirek/atmeneti-valtozas-az-oltasi-rendben/

§ http://www.agenziafarmaco.gov.it/sites/default/files/elenco_medicinali_carenti_25.01.2016.pdf

Country	Situation update as of	Source	Current or anticipated shortages	Impact on vaccination policy and mitigation		Comments	Impact (January 2016)
				Primary immunisation	Booster doses		
Lithuania	26 Jan. 2016	Communication to ECDC	**Current:** aP combination vaccines – DTaP-IPV/Hib, DTaP-IPV, Tdap Delayed delivery, reduced amount of delivered doses	**None**	**None**		
Liechtenstein							
Luxembourg	28 January 2016	Communication to ECDC	**Current**: DTaP-IPV/Hib shortage (summer 2015) Temporary shortage of DTaP-IPV	**Limited**: Pentavalent vaccine substitution with the same vaccine initially attributed to another country	**High**: Pre-school booster affected. DTaP-IPV temporary replaced by Tdap-IPV	Recurring DTaP-IPV/Hib shortage. Substitution with the same vaccine from the same manufacturer initially attributed to another country – issues relating to the language of the substitution vaccine notice (not an official language in Luxembourg, additional information required).	
Malta	26 Jan. 2016	Communication to ECDC	**None**	**None**	**None**		
Netherlands	26 Jan. 2016	Communication to ECDC	**None**	**None**	**None**		
Norway	26 Jan 2016	Communication to ECDC	Delayed delivery/reduced volume delivered for all aP-containing combination vaccines.	**None**	**None**	Safety supplies for some of the aP-containing combination vaccines are very limited.	
Poland	26 Jan 2016	Communication to ECDC	During 2015, delayed delivery and reduced volume delivered for all aP-containing combination vaccines. No issues with DTwP vaccines currently used in the national programme.	**Limited:** Postponement of the implementation of dose vaccination using aP-containing combination vaccines.	**High**: Delayed implementation of pre-school vaccination with aP-containing combination vaccines.		
Portugal	12 Mar 15	Technical advice request to ECDC	Shortage of combination vaccine with lower pertussis antigen content (aP-combo family). Impact on pre-school booster. ECDC provided technical advice to Portugal upon request.	-	-		
Romania	26 Jan 2016	Communication to ECDC	**Current:** shortage of hexavalent, tetravalent and dT/dTap vaccines	**High impact:** Lack of hexavalent vaccine and substitution with the same formulation vaccine but originally licensed for countries outside of EU.	**High:** Shortages of vaccines used as pre-school (tetravalent vaccine) and school (dT/dTap vaccine) boosters		
Slovakia	26 Jan. 2016	Communication to ECDC	**None**	**None**	**None**		
Slovenia	26 Jan 2016	Communication to ECDC	**None**	**None**	**None**		

Country	Situation update as of	Source	Current or anticipated shortages	Impact on vaccination policy and mitigation		Comments	Impact (January 2016)
				Primary immunisation	Booster doses		
Spain	26 Jan 2016	communication to ECDC	**Current:** shortage of pentavalent and dTap vaccines	**Limited:** Prioritisation of hexavalent vaccine for primary immunisation. Pentavalent vaccine to be prioritised for the second-year-of-life booster dose.	**High:** Booster at six years is delayed in a high proportion of children and immunisation for specific groups is interrupted. Prioritisation of vaccination during pregnancy in the whole country.		
Sweden	26 Jan 2016	Communication with ECDC	**Current:** Possible shortage from April, 2016 for DTaP-IPV	**None**	**None**	DTaP-IPV vaccine with expiration date 31 March 2016 is currently available.	
United Kingdom							

Legend
- *No status update communicated to ECDC in January 2016*
- *No shortage or impact on vaccination policy*
- *Limited shortage and/or limited impact on vaccination policy*
- *Significant shortage and/or significant impact on vaccination policy*

Annex 2. Pertussis vaccination schemes in the EU

All EU/EEA Member States have introduced vaccination against diphtheria, tetanus, poliomyelitis, pertussis and *Haemophilus influenzae* type b (Hib) in their primary infant schedules, with the majority of countries also administering vaccines against invasive pneumococcal disease and hepatitis B [13]. In addition, all EU/EEA Member States recommend vaccines against measles, mumps and rubella. Vaccination against meningococcal C infection (MenC) is recommended in 18 EU/EEA Member States.

The objectives of pertussis vaccination programmes are not to eliminate the disease but to prevent severe disease and deaths among youngest infants (<6 months):

- through direct protection by vaccinating infants soon after birth;
- through immunisation of those likely to infect young infants; and
- through maternal immunisation (implemented in a few EU/EEA countries).

Six weeks of age are generally considered as the minimum age to start DTwP/DTaP vaccination, with a primary immunisation schedule offering two to three doses in the first year of life [6]. Booster doses are usually offered from 11 months of age and throughout the second year of life, depending on the national vaccination schedules.

The current vaccination schedules in EU/EEA Member States are available from the ECDC vaccine schedule platform and are summarised in Table 2 [13]. Further details are available in the previous version of the RRA [1]

Table 2. Summary of vaccination schedules in the EU, adapted from the ECDC vaccine schedule platform

Schedule type	First year of life			Second year of life	Third year of life	Preschool booster	Adolescent booster	Country
'2p+1'	From 6 weeks to 6 months		Around first birthday					
	P1	P2	B1			B2	B3	F, IT, FI, NO, IS, SK
								SE*, DK, RO, AT
'3p+1'	P1	P2	P3	B1		B2	B3	BE, BG, CZ, EE, DE, GR, HU, LI, LU,
				B1		B2		HR, CY, LV, LI, MT, NL, PL, PT, SI, ES
				Hib-MenC combo	B1			UK
				Hib-MenC combo		B1	B2	IE
Vaccine combination generally used in EU/EEA	• DTaP-IPV-HepB/Hib ('hexavalent') • DTaP-IPV/Hib ('pentavalent') • DTaP-IPV ('tetravalent') • DTwP-IPV/Hib ('whole-cell pertussis combo')† • Hep B (used in conjunction with pentavalent)					• DTaP-IPV • TdaP • Tdap-IPV • Tdap	• Td • Tdap • Tdap-IPV	

P=primary dose; B=booster dose

The various immunisation schedules in Europe for acellular pertussis -containing vaccines (full-dose content) are based on experiences with whole-cell pertussis-containing vaccines (administered at two and three months, with a third dose given at four or six months).

Infant primary immunisation scheme

The current schedules in EU/EEA Member States for vaccination below 24 months of age with acellular pertussis-containing vaccines can be divided into the following groups:

- **A so-called '2p+1' schedule** corresponding to two doses of primary vaccination and a booster dose, with the vaccines given at three, five and 12 months (in AT, FI, IT, DK, SE, ICE, NO and SK) or at two, four and 11–12 months (in FR and RO).
- **A so-called '3p+1' schedule** corresponding to three doses given in the first year of life, starting as early as two months, with a booster in the second year of life (in BE, BG, HR, CY, CZ, EE, GE, GR, HU, LV, LI, LUX, MT, NL, PL, PT, SLO and ES).

* Starting in 2016, Sweden will include an adolescent booster dose in the national immunisation programme.

† Only in Poland

The only exceptions to these schedules are the UK and Ireland that – after primary vaccination at two, three and four months of age (UK) or at two, four and six months (IRE) – do not include a pertussis booster dose in the second year of life but rather between three and five years after primary immunisation.

All EU/EEA countries have shifted to acellular pertussis-containing vaccines except Poland, which still uses whole-cell pertussis-containing combination vaccines for primary immunisation and the first booster dose.

Vaccination policies for older age groups

School-age children and adolescents

The objective of the pre-school and adolescent booster is: i) to offer direct protection of those vaccinated by ensuring adequate circulating antibodies at protective levels in order to reduce the risk of infection due to waning immunity, ii) to limit the risk of infections of younger unprotected siblings in a household.

School entry

To date, all countries offer a booster dose around the time of school entry (so-called 'pre-school booster'). This booster dose is to account for reduced vaccine effectiveness observed among pre-school and school-age children [8]. The mechanisms involved are not entirely clear but there is a body of evidence in the EU, particularly in Italy and Sweden [14,15]. In Sweden, a two-dose priming schedule at three and five months of age, with a booster dose at 12 months, was adopted for primary immunisation. Findings from the long-term enhanced pertussis surveillance scheme indicated that waning immunity in the first DTaP-vaccinated cohorts lead to pertussis among 7- to 8-year-olds and demonstrated waning of vaccine-induced protection from pertussis. These findings led to the addition of a pre-school booster dose of acellular pertussis vaccine starting in 2007 [14,16].

During adolescence (11 to 18 years)

Seventeen EU/EEA Member State recommend booster doses during adolescence (11 to 18 years).

The objective of a dose given at this age is to extend protection until late adolescence and until childbearing age. There is little evidence of the impact on severe pertussis in infants but these strategies may have an impact on the targeted population and may decrease the circulation of the bacterium in the population at large. The indirect effect on infants is not well established [6].

Adults

Vaccination of adults can occur for different reasons:

- **As part of the regular booster policy:** Adults can be offered boosters of aP vaccine in combination with tetanus toxoid and reduced-dose diphtheria vaccine (TdaP) either once in their lifetime or every 10–20 years depending on the country (AT, BE, CZ, FR, DE, GR, IE, LI). Although these programmes (other than vaccination of pregnant women) have an impact on the directly targeted populations, there is as yet no substantial evidence that they have had a significant impact on severe pertussis in infants [6].
- **As part of the 'cocooning strategy':** Infants who are too young to be vaccinated are protected by vaccinating close contacts who could otherwise potentially become a source of infection. The cocooning strategy is recommended in some EU/EEA Member States (BE, FR, DE, LI). This strategy may have an impact on disease prevention in some settings if high vaccination coverage can be achieved in a timely manner. The overall impact and cost-effectiveness are likely to be substantially lower compare to maternal immunisation, which requires only one dose, whereas cocooning requires, as a minimum, multiple doses for parents and family members.
- **Maternal vaccination (during pregnancy):** A limited number of countries in the EU (Belgium, the UK, Ireland and Spain) have introduced maternal Tdap vaccination during pregnancy to help prevent mortality due to severe pertussis infection in infants too young to be vaccinated. A Tdap vaccine is used for vaccination during pregnancy.

Recent evidence consistently indicates that maternal immunisation with aP-containing vaccine during the third trimester of pregnancy is safe and highly effective in protecting infants from pertussis and that it may have a high positive impact on morbidity and mortality in infants too young to have been vaccinated. Experience in the UK with the vaccination of pregnant women indicates high impact on infant pertussis-related mortality. This outcome is probably primarily due to the direct protection conferred by the transfer of maternal antibodies, with some contribution from reduced risk of transmission through reduced likelihood of peripartum pertussis in the mother.

The point estimate for the vaccine effectiveness of maternal vaccination > 7 days before birth was 91% (95%, CI: 84%–95%) using the screening method, with adjusted vaccine effectiveness estimated at 93% (95%, CI: 81%–97%) in an associated case-control study [12,17,18]. However, a recent study in the UK showed that maternal immunisation can blunt the subsequent responses to some vaccines in the infant immunisation schedule. This phenomenon needs to be further monitored and could be possibly prevented by giving a booster dose of DTaP, Hib, MCC, and PCV-13 in the second year of life [19,20].

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List of background documents – April SAGE

Session 8: Missed Opportunities for Vaccination

Please find attached the following background documents for the missed opportunities session.

1. WHO Global Planning Guide for Assessing and Reducing Missed Opportunities (Draft)

WHO has recently updated the protocol and tools for conducting missed opportunities for vaccination (MOV) assessments, as well as the guidance for follow-up interventions/solutions. In collaboration with WHO Regional Offices, MOV assessments have been undertaken in Dominican Republic, Panama, Peru and Colombia (Bogota), Chad and Malawi and are in the planning stages for DRC, Mauritania, Kenya, Guinea, Timor Leste and Indonesia.

This *Planning Guide* provides a high-level overview of the WHO proposed strategy for assessing and reducing missed opportunities. It is targeted at national or district level managers, and will be accompanied by two additional documents: (a) a methodology/protocol document with generic questionnaires and field tools, targeted at the assessment/field team; and (b) an intervention guidebook that provides specific guidance for health facilities to translate the results of the field assessments into concrete actions to reduce missed opportunities for vaccination.

2. Two systematic literature reviews of missed opportunities for immunization that span a period of more than 30 years:

a) *Sridhar, et al. 2014. A systematic literature review of missed opportunities for immunization in low- and middle-income countries. Vaccine 32 (2014) 6870–6879*
b) *Hutchins, et al., 1993. Studies of missed opportunities for immunization in developing and industrialized countries; Bulletin of the World Health Organization, 71 (5): 549-560 (1993)*

These systematic reviews included 138 studies in more than 60 countries from all six WHO regions and provide the global perspective on missed opportunities by summarizing published data over more than 30 years. They present a strong justification for promoting the reduction of missed opportunities as a viable strategy to improve coverage and reduce equity, by demonstrating that: (1) the extent of missed opportunities have remained high (and unchanged) during the period of the review; (2) the underlying causes of missed opportunities have not changed significantly in the intervening years; (3) missed opportunities continue to occur in low, middle as well as high-income countries; and (4) that interventions to reduce missed opportunities are generally low-cost and feasible in most settings (such as emphasizing routine supervision and periodic in-service training of health workers; promoting simultaneous immunizations; facilitating integration of curative and preventive services; reinforcing information about true contraindications; and improving health workers' attitudes and practices).

DRAFT

Planning Guide to Reduce Missed Opportunities for Vaccination (MOV)

…For decision makers and programme managers at the national and subnational levels

Table of Contents

Introduction

Reducing missed opportunities for vaccination (MOV) is a strategy to increase immunization coverage, simply by making better use of existing vaccination sites (at health centres, hospitals, outreach/mobile services etc.).

The MOV strategy answers **three important questions**:

1. ***How many opportunities*** *for vaccination are missed at existing vaccination sites?*

2. ***Why*** *are opportunities for vaccination being missed at the different vaccination sites?*

3. ***What can be adjusted or done differently*** *(e.g. policies and behaviours) so that we do not miss any opportunity to vaccinate?*

Beyond improving immunization coverage, the aim of reducing MOVs is to improve health service delivery and promote synergy and integration among programmes.

What is a missed opportunity for vaccination (MOV)?

A missed opportunity for vaccination (MOV) includes any visit to a health facility by a child (or adult) who is unvaccinated, partially vaccinated or, not up-to-date, and free of contraindications to vaccination, which does not result in the person receiving all the vaccine doses for which he or she is eligible.

With the introduction of many new vaccines into national immunization schedules, the opportunities to vaccinate, as well as the opportunities to catch-up on delayed vaccinations during regular health service encounters, have both vastly increased.

About this guide

This guide is for decision-makers and national or district managers interested in using the MOV strategy to improve vaccine uptake and immunization coverage by reducing the number of missed opportunities for vaccination.

This guide gives a brief overview of the MOV strategy from beginning to end. It provides:

1. **Background information** on why reducing the number of missed opportunities can help to provide life-saving vaccines to a large number of children/persons who have not received any doses (unvaccinated) or who are not fully vaccinated (missing doses)

2. **The steps to plan and conduct** an assessment of missed opportunities and **how to analyze** and report on the results of an MOV assessment

3. **Guidance on how to use the findings of an MOV assessment to design and implement interventions** or solutions to reduce missed opportunities for vaccination

This ***Planning Guide*** is the first of three MOV documents that have been developed to be used together:

1. ***Planning Guide*** to Reduce Missed Opportunities for Vaccination (this document): *For use by decision-makers and programme managers at national and sub-national levels;*

2. Missed Opportunities for Vaccination ***Assessment Protocol***: Provides the detailed instructions, standard methodology, and tools for conducing field work, including: a training manual; sample questionnaires for the health facility exit interviews; health worker knowledge, attitude, and practice (KAP) questionnaire; and detailed guidance for conducting key informant interviews and focus group discussions.

3. ***MOV Intervention Guidebook***: This provides guidance for translating the findings of the MOV assessments into actionable work plans. It includes: a list of frequently found reasons for MOVs; a list of potential interventions to reduce MOVs; health facility level guidance for working through facilitator-led activities and processes for exploring locally tailored interventions to reduce MOVs. The MOV Intervention Guidebook could also be used as a stand-alone guide for assessing and reducing MOVs in selected health facilities where the standard assessments are yet to be conducted.

How can the MOV strategy increase immunization coverage?

The MOV strategy is about establishing a system so that any child/person eligible for vaccination who comes to a health facility/mobile health service (for whatever reason), receives the needed vaccines during their visit.

Missed opportunities for vaccination occur:

1. During visits to health facilities/mobile health services for immunization (immunization contact), as well as

2. During visits to health facilities/mobile health services for curative services (e.g. treatment of mild fever, cough, diarrhoea, bruises) or other preventive services (e.g. growth monitoring, nutrition assessments and oral rehydration training sessions, etc.);

How much could immunization coverage increase if MOVs were reduced?

Reducing MOV can contribute towards achieving the 2020 Global Vaccine Action Plan (GVAP) goal of "90% national coverage and 80% in every district or equivalent administrative unit, for all vaccines in the national immunization schedule."

A 2014 analysis[1] using data from recent DHS and MICS surveys estimated the potential gains in coverage if the children who were in contact with health services received the doses of vaccine(s) that were due. For example, bridging the MOV gap could potentially improve Penta/DTP3 coverage by as much as 10 percentage points, depending on the country (Table 1). At a sub-national level (e.g. poor performing districts or facilities) these coverage gains could be even greater.

Recent field assessments of the magnitude of MOV in AMR (2014) and AFR (2015) regions of the WHO have shown that between 23% to 96% of eligible children who visited a health facility for vaccination or for medical care, left the health facility without receiving the vaccine doses that they needed. These are children who are already being reached by health services (and not necessarily so-called "hard-to-reach" or underserved populations). Missing the opportunity to vaccinate these children, when they are already present at the health facility/outreach site, is unacceptable.

[1] Unpublished data. WHO analysis of potential coverage gains if missed opportunities were eliminated, using recent DHS and MICS surveys and other ancillary data.

Table 1: Current and estimated 2013 DTP3 coverage by country, if missed opportunities for vaccination were to be completely eliminated

Country	*WUENIC DTP3 (2013)**	*Estimated DTP3 (2013)***
Benin	69	77
Cambodia	92	95
Chad	48	*[2]
DRC	72	80
Ghana	90	92
India	72	84
Kenya	76	81
Liberia	89	95
Malawi	89	96
Mauritania	80	*[3]
Mozambique	78	92
Niger	70	80
Sierra Leone	92	97
Tanzania	91	99
Uganda	78	89
Zambia	79	88

Table 1 footnotes:
* WHO-UNICEF best estimates of national immunization coverage.
** Using estimates (from recent DHS and MICS) of the proportion of un-/under-vaccinated children who had visited a health facility for treatment of cough, fever and diarrhea in the preceding two weeks, we estimated what the national DTP3 coverage would have been, had they all used the health visit to take all the vaccines for which they were eligible. Such a healthcare encounter was considered a missed opportunity only if the missed vaccine dose was more than 3 months overdue and there were no contraindications to vaccination.

What are the core principles of the MOV strategy?

Principle #1. Focuses on implementing actions at the local level, where most of the reasons for missed opportunities for vaccination are identified

The MOV strategy relies on a bottom-up approach that obtains information on the reasons for MOV from service providers and the users of health services, at the facility level. It then seeks their commitment and knowledge to resolve the identified issues. When health workers and

[2] Insufficient data from recent DHS to calculate estimated DTP3 coverage
[3] Insufficient data from recent DHS to calculate estimated DTP3 coverage

local communities take ownership and responsibility for reducing missed opportunities, the impact on number of children vaccinated is intensified.

Principle #2. Emphasizes country leadership

In order to achieve long-term gains, the MOV strategy in each country begins with an assessment of why opportunities for vaccination are missed and then specifically addresses them using locally-tailored interventions. The MOV strategy is designed to be low-cost and action oriented, and is intended to be fostered by the national and sub-national level, but mostly implemented and managed by the health facility staff. MOV assessments should not be performed as stand-alone research projects by an academic institution; rather every effort should be made to have the EPI team incorporate reducing MOV in their programme improvement plans and to use it to optimize health service processes, policies and mechanisms.

Principle #3. Capitalizes on existing platforms and builds synergies

The MOV strategy should be integrated with other ongoing country work plans and activities for increasing routine vaccine coverage and equity. For instance, where applicable, the MOV strategy can be built into health systems strengthening activities, as it promotes synergies with other programmes. The focus on health facilities seeks to improve the management, organization and integration of service delivery at the lowest level possible. As a result, the coverage of other health services can also be improved.

Principle #4. Invests in sustainable monitoring and supervision

Reducing MOV requires an investment in regular monitoring of coverage and frequent supportive supervision from the next level of the health system. It is important to monitor the number of children vaccinated, and compare this from month to month, as well as compare similar months from year to year. The monitoring charts should be large enough to be displayed and visible to all users of the health facility as well as for review during community meetings. (Figure: attach example of community monitoring template from SE Asia?).

What are the steps for implementing the MOV strategy?

There are ten steps in the MOV strategy, each leading naturally to the next. These 10 steps are summarized below:

Step 1: Plan for an MOV assessment and intervention

Step 2: Prepare for the assessment and secure commitment for follow-up interventions

Step 3: Conduct field work for the rapid assessment of MOV

Step 4: Analyze preliminary data and develop draft recommendations

Step 5: Brainstorm on proposed interventions and develop a work plan for the interventions

Step 6: Debrief with MOH leadership and immunization partners on proposed next steps

Step 7: Implement the interventions

Step 8: Provide supportive supervision and monitor progress

Step 9: Conduct rapid field evaluation of outcomes/impact of interventions (6-12 months later)

Step 10: Incorporate into long term plans to ensure gains are sustainable.

For each step, this *Planning Guide* outlines the key actions that need to be taken and any lessons learned from country experiences. The ten steps are further categorized into:

1. Steps to be completed by the planning team at the national and subnational level:
    - Steps 1 – 2;
    - Steps 7 – 10;
2. Steps to be completed by the field team responsible for conducting and analyzing the assessments:
    - Steps 3 – 6;

Overview Table of the MOV Strategy:

	For the *Planning Team* at national and subnational level		For the *Field Team* conducting and analyzing the assessment				For the *Planning Team* at national and subnational level			
	Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 6**	**Step 7**	**Step 8**	**Step 9**	**Step 10**
What	***Plan for an MOV assessment and intervention***	***Prepare for the assessment and secure commitment for follow-up interventions***	***Conduct field work for the rapid assessment of MOV***	***Analyze preliminary data and develop draft recommendations***	***Brainstorm on proposed interventions and develop a work plan for the implementation***	***Debrief with MOH leadership and immunization partners on proposed next steps***	***Implement the interventions***	***Provide supportive supervision and monitoring***	***Conduct rapid field evaluation of outcomes/impact of interventions***	***Incorporate into long term immunization plans to ensure gains are sustainable***
Who	MOH, with support from WHO (CO, RO)	MOV Planning Team, MOH, WHO and other key immunization partners	Assessment coordinator, MOH and in-country immunization partners	Assessment coordinator and representatives from MOH and partner organizations	Assessment coordinator, field supervisors and MOH-EPI leadership (health facility, district and/or national level)	All immunization partners, with leadership by MOH	Health facility staff, MOH and immunization partners	MOH, WHO and other key immunization partners	MOH, WHO and other key immunization partners	MOH, WHO and other key immunization partners
Timing/ Duration	2–4 months before field work	1-2 months before field work	1-2 weeks duration, depending on training needs and travel distances	1-2 days	1 day	½ day	6-12 months	3-12 months	6-12 months following Step 7/8	Ongoing
Tasks	**Task 1.1** Decide that an MOV strategy is needed **Task 1.2** Achieve high-level support from the MOH **Task 1.3** Identify an Assessment Coordinator and members of the MOV Planning Team (preferably	**Task 2.1** Collect, compile and review available information on the immunization program, including recent program reviews and coverage estimates **Task 2.2** Decide on the scale of the MOV work (national or selected districts(s)) **Task 2.3** If appropriate, select subnational areas for field	**Task 3.1** Print questionnaires and/or prepare electronic tablets or smartphones for electronic data collection **Task 3.2** Train supervisors and interviewers on assessment process and logistics **Task 3.3** Administer exit assessments to the mothers/caregivers	**Task 4.1** Tally data from sampled questionnaires for analysis, or download preliminary data from the electronic data collection platform **Task 4.2** Collate the facilitator notes taken during the qualitative interviews	**Task 5.1** Present the preliminary data from ***Step 4*** and ask for reactions from the group **Task 5.2** Facilitate a discussion on ideas for reducing MOVs in the selected district(s)/the entire country	**Task 6.1** Present the summary objectives of the assessment, the process of the field work and the updated results and recommendations from ***Step 5*** **Task 6.2** Present the	**Task 7.1** Based on the findings of the MOV assessment, implement interventions to address specific findings, e.g. additional tailored trainings; mass media to build community demand; etc. **Task 7.2** Provide additional policy guidance,	**Task 8.1** Establish a clear monitoring and supportive supervision plan **Task 8.2** Provide funds for supportive supervision and corrective actions **Task 8.3** Provide monitoring charts and ensure compliance with visible display of monthly coverage	**Task 9.1** Following 6-12 months of implementation of activities, conduct evaluation of effectiveness of the interventions in selected health facilities	**Task 10.1** To ensure sustainability, include interventions to reduce MOV in long-term immunization plans (e.g. cMYP and annual EPI plans)

	For the *Planning Team* at national and subnational level		For the *Field Team* conducting and analyzing the assessment				For the *Planning Team* at national and subnational level			
	Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 6**	**Step 7**	**Step 8**	**Step 9**	**Step 10**
What	***Plan for an MOV assessment and intervention***	***Prepare for the assessment and secure commitment for follow-up interventions***	***Conduct field work for the rapid assessment of MOV***	***Analyze preliminary data and develop draft recommendations***	***Brainstorm on proposed interventions and develop a work plan for the implementation***	***Debrief with MOH leadership and immunization partners on proposed next steps***	***Implement the interventions***	***Provide supportive supervision and monitoring***	***Conduct rapid field evaluation of outcomes/impact of interventions***	***Incorporate into long term immunization plans to ensure gains are sustainable***
	multi-partner; may be a sub-committee of the Inter-agency Coordinating Committee (ICC) or similar body) **Task 1.4** Identify funding sources from within and/or outside the EPI program **Task 1.5** Prepare a schedule of activities and include in annual work plan, with approval of the Inter-agency Coordinating Committee (ICC) or similar body	work **Task 2.4** Agree on sample size, the number of field staff needed and the number of days for field work **Task 2.5** Finalize the budget for the assessment field work **Task 2.6** Prepare a draft budget for the post-assessment interventions **Task 2.7** Share plan with ICC or appropriate body (and partners) for final approval of the plan **Task 2.8** Clarify whether ethical approval is necessary and commence the process. **Task 2.9** Review generic questionnaires, and if necessary adapt to country context and vaccination	of children less than two years old, in the selected health facilities **Task 3.4** Administer health worker KAP (knowledge, attitude and practices) assessment **Task 3.5** Conduct focus group discussions for mothers/caregivers **Task 3.6** Conduct focus group discussions for health workers **Task 3.7** Conduct key informant interviews with the pre-determined number of senior staff and health administrators **Task 3.8** Extract vaccination	**Task 4.3** Conduct a quick-and-dirty analysis of preliminary data, to identify key themes and major results for discussion in ***Step 5*** **Task 4.4** Prepare for detailed analysis of complete data, as well as data cleaning (Cross-reference: **Annex 8, MOV Protocol)**	**Task 5.3** Propose a detailed framework, work plan and chronogram for reducing MOVs over the next 6-12 months **Task 5.4** Assign roles and responsibilities to different partners using the work plan from Task 5.3, including a clear supervision, monitoring and evaluation plan **Task 5.5** Propose existing systems, opportunities and activities to ensure community	proposed work plan and request feedback and/or endorsement of the work plan from the MOH and partner leadership **Task 6.3** During the debrief, commence discussions on funding of the interventions or including them in existing immunization or health system improvement plans	directives, job aids and other communication materials from the national level **Task 7.3** Using the MOV Intervention Guidebook as a starting point (Cross-reference), encourage local/tailored solutions for reducing MOVs in each health facility	estimates		

	For the *Planning Team* at national and subnational level		For the *Field Team* conducting and analyzing the assessment				For the *Planning Team* at national and subnational level			
	Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 6**	**Step 7**	**Step 8**	**Step 9**	**Step 10**
What	***Plan for an MOV assessment and intervention***	***Prepare for the assessment and secure commitment for follow-up interventions***	***Conduct field work for the rapid assessment of MOV***	***Analyze preliminary data and develop draft recommendations***	***Brainstorm on proposed interventions and develop a work plan for the implementation***	***Debrief with MOH leadership and immunization partners on proposed next steps***	***Implement the interventions***	***Provide supportive supervision and monitoring***	***Conduct rapid field evaluation of outcomes/impact of interventions***	***Incorporate into long term immunization plans to ensure gains are sustainable***
		schedule **Task 2.10** If needed, finalize arrangements for the translation of the updated questionnaires and training materials into the local language(s)	data from health facility registers for children with no vaccination cards		participation during the intervention phase					
Expected outcomes	- High level commitment from MOH - MOV strategy listed in the annual EPI work plan - National Planning Team for MOV constituted	- Finalized chronogram for MOV activities - Finalized budget for MOV assessment - Draft budget for MOV post-assessment interventions - Exemption from ethical approval process, or approval, as appropriate - Finalized questionnaires and training materials for field work training (including plans for translation, if needed)	- Printed questionnaires and interview guides - Field staff fully trained on assessment process - Field staff proficient in completing the questionnaires on paper as well as on the tablets - Completed exit interviews, KAP assessments and qualitative interviews (focus group discussions and key informant interviews)	- Basic frequencies from the questionnaire data to elicit discussions in ***Step 5*** - Critical quotes from the focus group discussions that capture the essence of the key findings - A list of proposed interventions to reduce MOVs from all assessment components	- List of proposed activities to reduce MOVs (to be prioritized by MOH) - Frame work and 6-12 month work plan for reducing MOVs - Outline of roles and responsibilities of different partners	- Finalized recommendations - Finalized and endorsed work plan, with clear implementation timelines - Catalytic funding and/or plans for integration with existing programs - Plans for social mobilization and communication materials	- Interventions implemented nationally or in selected districts/health facilities	- Supportive supervision reports with corrective measures - Monitoring charts duly completed and visibly displayed in all health facilities	- Reduction in MOVs reported in evaluations - Increase in number of children vaccinated when compared to previous year's numbers - Reduction of MOVs and general health service improvement are ingrained as a routine process in evaluated health facilities - Results of evaluations shared with ICC or similar body	- MOV interventions and processes included as part of country plans such as cMYP and annual EPI plans - Funding is available for implementation

STEP 1: Plan for an MOV Assessment

STEP 1: Plan for an MOV assessment and intervention
Task 1.1: Decide that an MOV strategy is needed
Task 1.2: Achieve high-level support from the MOH
Task 1.3: Identify an Assessment Coordinator and members of the MOV Planning Team (preferably multi-partner; may be a sub-committee of the Inter-agency Coordinating Committee (ICC) or similar body)
Task 1.4: Identify funding sources from within and/or outside the EPI programme
Task 1.5: Prepare a schedule of activities and include in annual work plan, with approval of ICC or similar body

Task 1.1: Decide that an MOV strategy is needed

The causes of missed opportunities for vaccination and the interventions to reduce them vary widely in different countries. Experience from countries where the strategy has been implemented, shows that the MOV strategy and tools are applicable across low-, medium- and high-coverage immunization programmes. Each country needs to critically appraise the findings of its recent immunization programme reviews and decide whether addressing MOV will be a useful strategy to increase immunization coverage.

Task 1.2: Achieve high-level support from the MOH

Once **Task 1.1** is completed, the EPI programme should put together a detailed plan to obtain high-level MOH support. Such a support is usually obtained by making presentations to the MOH leadership that include: a listing of some of the known problems with the immunization programme and how the MOV strategy could provide solutions; a listing of possible sources of funding, such as an upcoming Health Systems Strengthening (HSS) application or similar funds; etc.. This task is critical for the post-assessment phase, when new activities and policy changes may require high-level political support for sustainable funding and implementation.

Task 1.3: Identify an *Assessment Coordinator* and members of the *MOV Planning Team* (preferably multi-partner; may be a sub-committee of the Inter-agency Coordinating Committee [ICC] or similar body)

Identifying MOV champions early in the planning phase is one of the critical steps for success. The Assessment Coordinator may be the EPI Manager or other official from the MOH or WHO Country Office. Ideally, the MOV Planning Team should include a representative from each of the key immunization partners, for example, one person each from the MOH, WHO and UNICEF. A team of 3 – 5 persons is ideal. This does not need to be a new committee, but could be a sub-committee/working group of the ICC or similar body.

Task 1.4: Identify funding sources from within and/or outside the EPI programme

Although the cost of MOV field work is not very high, it is necessary to identify potential sources of funding for the field work as well as the post-assessment interventions. This is to ensure that the entire MOV strategy can be fully implemented. Conducting the MOV assessment and determining the causes of MOV (Steps 3-6), without supporting the implementation and monitoring of corrective interventions/actions (Steps 7-10) is a failure of the strategy. For long-term funding of intervention and supervision activities, explore early synergies with existing (funded) programmes and/or other platforms (e.g. HSS funds) to enhance sustainability.

Task 1.5: Prepare a schedule of activities and include in annual work plan, with approval of ICC or similar body

The final task in the planning phase is to ensure that the ICC or similar high-level body backs the activities proposed. Country experience shows that including the MOV assessment and interventions in an annual EPI work plan, remarkably improves the chances that sufficient time and resources are allocated for its implementation.

STEP 2: Prepare for the assessment and secure commitment for follow-up interventions

STEP 2: Prepare for the assessment and secure commitment for follow-up interventions
Task 2.1: Collect, compile and review available information on the immunization programme, including recent programme reviews and coverage estimates
Task 2.2: Decide on the scale of the MOV work (national or selected districts(s))
Task 2.3: If appropriate, select subnational areas for field work
Task 2.4: Agree on sample size, the number of field staff and the number of days for field work needed
Task 2.5: Finalize the budget for the assessment field work
Task 2.6: Prepare a draft budget for the post-assessment interventions
Task 2.7: Share plan with ICC or appropriate body (and partners) for final approval of the plan
Task 2.8: Clarify whether ethical approval is necessary and commence the process.
Task 2.9: Review generic questionnaires, and if necessary adapt to country context and vaccination schedule
Task 2.10: If needed, finalize arrangements for the translation of the updated questionnaires and training materials into the local language(s)

Task 2.1: Collect, compile and review available information on the immunization programme, including recent programme reviews and coverage estimates

Where available, recent coverage survey and programme review reports are invaluable in preparing for the MOV assessments, particularly for prioritizing districts or areas to focus the interventions.

Task 2.2: Decide on the scale of the MOV work (national or selected districts(s))

The MOV methodology is adaptable to different levels of the health care system. This is because the solutions to the problems identified are mostly applicable at the service delivery point, but national policies and guidelines may sometimes need to be modified. It is noteworthy that even though the assessments may be performed in a limited number of sentinel districts/health facilities, the follow-up interventions may be scaled-up nationwide.

Task 2.3: If appropriate, select subnational areas for field work

Some countries have selected the largest or worst-performing districts for the MOV assessments and interventions, with the understanding that this would provide the greatest benefit as well as the best use of limited resources.

Task 2.4: Agree on sample size, the number of field staff needed and the number of days for field work

Decisions about sample size and scope will likely be impacted by the availability of financial, human and time resources. Selection of districts is expected to be performed at the national level, by the MOV Planning Team. If a national sample is being selected, the MOV assessment should include 8–10 districts.

Independent of the number of districts selected, the following principles should be applied (For more details, cross-reference: *MOV Protocol*, Section 8.2):

1. At least 300–500 observations are necessary for any meaningful analysis and interpretation of the exit survey data;
2. Data collection should be spread across several unique health facilities (for example, 10 interviews in each of 50 health facilities [n=500], rather than 25 interviews in each of 20 health facilities [n=500]);
3. Where possible, a mix of health facilities should be assessed, in terms of size (small/medium/large), type (private/public) and location (rural/urban), etc.;

Task 2.5: Finalize the budget for the assessment field work

Based on the decisions in Task 2.4 (above), a budget should be fairly easy to work out. It is important to include costs associated with the training of field staff, printing of materials, and daily transport during field work. (Cross-reference: Example budget template in Annex 6 of the *MOV Protocol*).

Task 2.6: Prepare a draft budget for the post-assessment interventions

In addition to the MOV assessment budget, it is advisable at this stage to start preliminary discussions around different cost scenarios for potential interventions, given what is known about the performance of and bottlenecks in the immunization programme. Possible funding sources should be contacted at this time. The inclusion of potential funders in the planning and assessment phases increases the likelihood that they will be able to fund the needed interventions. In addition, such early engagement may necessitate modifications in the design of the MOV assessment to meet funding requirements.

Task 2.7: Share plan with ICC or appropriate body (and partners) for final approval of the plan

At the next meeting of the ICC, the MOV Planning Team should present the proposed plan, budget and timelines for approval. The primary purpose of the MOV assessment is to use the data and results for action (e.g. adapt policies, processes) and design corrective interventions/solutions that will reduce MOVs. Solid endorsement from such a body is therefore a critical factor for success.

Task 2.8: Clarify whether ethical approval is necessary and commence the application process.

In most countries, the MOV assessment has been undertaken as a routine programme evaluation. In such situations, it may be exempted from formal ethical clearance. This should be clarified with the responsible body as early as possible.

Task 2.9: Review generic questionnaires, and if necessary adapt to country context and vaccination schedule

With leadership from the Assessment Coordinator, the MOV Planning Team should review and adapt the generic exit interview questionnaire (Cross-reference: *MOV Protocol*, Annex 2) and Health Worker KAP Questionnaire (Cross-reference: *MOV Protocol*, Annex 3) to the country context. Such adaptations may include updating the generic questionnaires with the local vaccination schedule, health facility and health worker classifications, etc. Comparability of the results with other country assessments should be kept in mind during these adaptations.

Task 2.10: If needed, finalize arrangements for the translation of the updated questionnaires and training materials into the local language(s)

If needed, translation of all instruments should commence as soon as possible. This is because training cannot start until translation is completed and validated. In addition, if electronic data collection is planned, the time needed to programme the translated questionnaires into the software in the electronic tablets or smart phones should be accounted for.

STEP 3: Conduct field work for the rapid assessment of MOV

STEP 3: Conduct field work for the rapid assessment of MOV
Task 3.1: Print questionnaires and/or prepare electronic tablets or smartphones for electronic data collection
Task 3.2: Train supervisors and interviewers on assessment process and logistics (3 days)
Task 3.3: Administer exit surveys to the mothers/caregivers of children less than two years old, in the selected health facilities (2–3 days)
Task 3.4: Administer health worker KAP (knowledge, attitude and practices) assessment (2–3 days)
Task 3.5: Conduct focus group discussions for mothers/caregivers (1/2 day)
Task 3.6: Conduct focus group discussions for health workers (1/2 day)
Task 3.7: Conduct key informant interviews with the pre-determined number of senior staff and health administrators (1/2 day)
Task 3.8: Extract vaccination data from health facility registers for children with no vaccination cards (1/2 day)

(Cross-reference: Please see details of field work implementation in the *MOV Protocol, Section* 8).

The MOV strategy uses a bottom-up approach that seeks to assess the reasons for missed opportunities as well as potential interventions at the vaccination point - from the service providers and the mothers/caregivers. The assessment strategy uses triangulation from multiple assessment components, as listed in the schematic below:

Step 3 (Tasks 3.1-3.8): Schematic for understanding the contributions of the five assessment components

Expected outcomes	Assessment components
A. Identify the magnitude, extent and causes of missed opportunities	1. Health facility exit interviews (interviewer-administered) 2. Health worker KAP interviews (self-administered) 3a. Focus group discussions (for caregivers and health workers) 4a. Key informant interviews (for health administrators)
B. Identify potential interventions to reduce MOVs	3b. Focus group discussions (for caregivers and health workers) 4b. Key informant interviews (for health administrators) 5. Work group brainstorming sessions

STEP 4: Analyze preliminary data and develop draft recommendations

STEP 4: Analyze preliminary data and develop draft recommendations
Task 4.1: Tally data from sampled questionnaires for analysis, or download preliminary data from the electronic data collection platform
Task 4.2: Collate the facilitator notes taken during the qualitative interviews
Task 4.3: Conduct a quick-and-dirty analysis of preliminary data, to identify key themes and major results for discussion in ***Step 5***
Task 4.4: Prepare for detailed analysis of complete data, as well as data cleaning (Cross-reference: Annex 8, *MOV Protocol*)

Task 4.1: Tally data from sampled questionnaires for analysis, or download preliminary data from the electronic data collection platform

If the Assessment Coordinator is familiar with a simple analytic software such as *Visual Dashboard* in EPIInfo, this is ideal for quick analysis and for drawing and updating simple charts automatically. Listing of simple frequencies is all that is needed at this time.

Experience in countries that have completed the MOV assessments shows that this step is facilitated by the use of electronic data collection platforms (electronic tablets or smartphones). When possible, use of such electronic platforms is highly encouraged.

Task 4.2: Collate the facilitator notes taken during the qualitative interviews

If a social scientist is a part of the Field Team, they would be responsible for conducting the qualitative interviews. They can submit preliminary analysis results and important quotes for inclusion in the presentation for the brainstorming (**Step 5**) and debrief sessions (**Step 6**). Otherwise, Assessment Coordinator should compile important quotes and themes discussed during the focus group discussions for presentation.

Task 4.3: Conduct a quick-and-dirty analysis of preliminary data, to identify key themes and major results for discussion in *Step 5*

Together with the MOV Planning Team, the Assessment Coordinator should compile the results from the different assessment components into a set of presentation slides. It should be emphasized that these data and results are preliminary. However, experience shows that the final results rarely differ markedly. Please note that it will be nearly impossible to derive an "estimate" of the proportion of children missed at this stage of the analysis. This requires further data cleaning, reclassification and subgrouping (Task 4.4).

Task 4.4: Plan for detailed analysis of complete data, as well as data cleaning (Cross-reference: Annex 8 of the Protocol)

Detailed data analysis should commence as soon as possible after the debrief, and certainly final results should feed into the planning of the post-assessment interventions. If analysis cannot be performed in-country due to time and capacity constraints, it should be outsourced as soon as possible.

STEP 5: Brainstorm on proposed interventions and develop a work plan for the implementation

STEP 5: Brainstorm on proposed interventions and develop a work plan for the interventions
Task 5.1: Present the preliminary data from ***Step 4*** and ask for reactions from the group
Task 5.2: Facilitate a discussion on ideas for reducing MOVs in the selected district(s)/the entire country
Task 5.3: Propose a detailed framework, work plan and chronogram for reducing MOVs over the next 6 -12 months
Task 5.4: Assign roles and responsibilities to different partners using the work plan from Task 5.3, including a clear supervision, monitoring and evaluation plan
Task 5.5: Propose existing systems, opportunities and activities to ensure community participation during the intervention phase

Task 5.1: Present the preliminary data from *Step 4* and ask for reactions from the group

A facilitated open discussion format with note-taking is encouraged for this task.

Task 5.2: Facilitate a discussion on ideas for reducing MOVs in the selected district(s)/the entire country

We suggest the following **ideas** for conducting effective brainstorming sessions:

- Present the key findings to the entire group;
- Split the group into separate working groups (WG):
  - Each WG should consist of 3-5 participants;
- Each group to discuss two aspects of the approach – potential interventions and the chronogram of activities over the next 6-12 months;
  - To the extent possible, each idea should leverage existing funding streams and country plans;
- Identify Technical Assistance needs and indicate clear timelines, etc.;
- At the end of the WG sessions, each WG will present their discussions to the plenary:
  - For input and synthesis in preparation for final debrief;
  - PowerPoint templates will be provided;

Task 5.3: Propose a detailed framework, work plan and chronogram for reducing MOVs over the next 6-12 months

Following the discussions in Task 5.2, compile ideas from all working groups into an integrated list of activities, responsible persons and timelines for the debrief presentation. (Cross-reference: See a generic example in Annex 9 of MOV Protocol).

Task 5.4: Assign roles and responsibilities to different partners using the work plan from Task 5.3, including a clear supervision, monitoring and evaluation plan

Ensure that immunization partners with expertise in different aspects of the programme are willing to take their respective roles and responsibilities (e.g. communications, health worker trainings, improvements in the cold chain, funding of interventions, etc.).

Task 5.5: Propose existing systems, opportunities and activities to ensure community participation during the intervention

Long-term sustainability of immunization programmes require ongoing community participation and community demand for high quality services. Plan to invite community service organizations (CSOs) and community development committees to the final debrief session (Step 6). Use the opportunity to solicit their input and assistance with implementing the proposed interventions.

STEP 6: Debrief with MOH leadership and immunization partners on proposed next steps

STEP 6: Debrief with MOH leadership and immunization partners on proposed next steps
Task 6.1: Present the summary objectives of the assessment, the process of the field work and the updated results and recommendations from ***Step 5***
Task 6.2: Present the proposed work plan and request feedback and/or endorsement of the work plan from the MOH and partner leadership
Task 6.3: During the debrief, commence discussions on funding of the interventions or including them in existing immunization or health system improvement plans

Task 6.1: Present the summary objectives of the assessment, the process of the field work and the updated results and recommendations from *Task 5*

The objectives and results of the assessment components and the districts covered should be presented in a set of PowerPoint slides.

Task 6.2: Present the proposed work plan and request feedback and/or endorsement of the work plan from the MOH and partner leadership

Sufficient time should be allocated to discussion of the proposed work plan. Additional ideas should be included and a final version should be endorsed by the end of the debrief.

Task 6.3: During the debrief, commence discussions on funding of the interventions or inclusion in existing immunization or health system improvement plans

To ensure that the proposed intervention activities are implemented in a timely manner, concrete discussions on new funding sources or the re-programming of existing funds should commence during the debrief. In addition, new ideas for including the MOV strategy in upcoming funding applications should be explored.

STEP 7: Implement the interventions

STEP 7: Implement the interventions
Task 7.1: Based on the findings of the MOV assessment, implement interventions to address specific findings, e.g. additional tailored trainings; mass media to build community demand; etc. **Task 7.2:** Provide additional policy guidance, directives, job aids and other communication materials from the national level **Task 7.3:** Using the *MOV Intervention Guidebook* as a starting point (Cross-reference), encourage local/tailored solutions for reducing MOVs in each health facility

Task 7.1: Based on the findings of the MOV assessment, implement interventions to address specific findings, e.g. additional tailored trainings; mass media to build community demand; etc.

It is important that the proposed interventions to reduce MOVs target the problems that were identified during the assessment. These problems may differ by district or by type of health facility (e.g. urban/rural or public/private).

Task 7.2: Provide additional policy guidance, directives, job aids and other communication materials from the national level

The MOV Planning Team should work with the MOH and ICC to institute policy and other types of guidance to address specific issues, e.g. on vaccination of children who are older than 24 months, implementation of the open vial policy, contra-indications, etc. Measures to ensure that such new or updated policies are implemented at the vaccination point should be addressed.

Task 7.3: Using the *MOV Intervention Guidebook* as a starting point (Cross-reference), encourage local/tailored solutions for reducing MOVs in each health facility

The *MOV Intervention Workgroup* provides guidance and options for interventions at the national, district or health facility level. The MOV Intervention Guidebook should assist the MOV Planning Team in designing workable solutions for the country at the different levels of the health system. It also provides suggestions for supportive supervision, monitoring and evaluation of proposed activities.

STEP 8: Provide supportive supervision and monitor progress

STEP 8: Provide supportive supervision and monitoring
Task 8.1: Establish a clear monitoring and supervision plan **Task 8.2:** Provide funds for supportive supervision and corrective actions **Task 8.3:** Provide monitoring charts and ensure compliance, with visible display of monthly coverage estimates

Please refer to the *MOV Intervention Guidebook* for additional details (Cross-reference).

Task 8.1: Establish a clear monitoring and supervision plan

The focus of the supervisory visits should be on correcting any identified implementation problems. To avoid duplication of efforts, the monitoring and supervision plan should strengthen existing systems whenever possible. These need to be systematized and regular, preferably monthly and from the next level of the health system. Templates for reporting to higher levels should be provided and a collation method should be established for onward reporting and feedback.

Task 8.2: Provide funds for supportive supervision and corrective actions

It should be emphasized that the supervisory visits should not be designed merely for reporting to higher levels. In most countries, additional funding for supervisory visits may be required at the initial phases, and these should be budgeted for as appropriate. Similarly, corrective actions may require funds for implementation, and these should be accounted for in the intervention budget.

Task 8.3: Provide monitoring charts and ensure compliance, with visible display of coverage estimates

Clear and easy-to-use wall monitoring charts should be printed centrally and distributed to all health facilities. The charts should provide a blank space for personalization, such as facility/village name, date, etc. Emphasis should be placed on numerator tracking for different antigens, as this is sufficient to monitor changes from month to month, or to compare with similar months from previous years. Examples of charts are provided in the MOV Intervention Guidebook.

STEP 9: Conduct rapid field evaluation of outcomes/impact of interventions (6-12 months later)

STEP 9: Conduct rapid field evaluation of outcome/impact of interventions (6-12 months later)
Task 9.1: Following 6-12 months of implementation of activities, conduct evaluation of effectiveness of the interventions in selected health facilities

Following 6-12 months of implementation of interventions and supportive supervision, a re-assessment of MOVs should be conducted in (a subset of) the original health facilities (Step 3). This evaluation should use a similar methodology as the initial assessment. The objective is to assess any changes in practice styles and vaccination coverage that may have occurred as a result of the interventions. The MOV Planning Team should ensure that the results of this evaluation are shared widely and that the MOH leadership are updated with the outcomes.

As an ancillary assessment, if there was no MOV interventions in some parts of the country, such areas could serve as controls to further illustrate the impact of the interventions on service quality and vaccine coverage.

STEP 10: Incorporate into long term immunization plans to ensure gains are sustainable.

STEP 10: Incorporate into long term immunization plans to ensure gains are sustainable
Task 10.1: To ensure sustainability, include interventions to reduce MOV in long-term immunization plans (e.g. cMYP and annual EPI plans)

The MOV strategy should not be conceived as a one-time activity to increase vaccine coverage, rather as a health system-wide service integration effort to improve vaccination as well as other health services. As such, from the outset, the MOV Panning Team should ensure that MOV activities and processes are included as part of country plans such as the cMYP and the annual EPI plans. The intervention activities should be routinized and sustained, by ensuring the availability of sufficient funding and political will. Periodic supportive supervision and monitoring of MOVs should continue on a monthly or quarterly basis, as part of the monitoring and supervision plan for health services in general.

Studies of missed opportunities for immunization in developing and industrialized countries

S.S. Hutchins,[1] H.A.F.M. Jansen,[2] S.E. Robertson,[3] P. Evans,[4] & R.J. Kim-Farley[5]

Missed opportunities for immunization are an obstacle to raising immunization coverage among children and women of childbearing age. To determine their global magnitude and reasons, studies reported up to July 1991 were reviewed. A standard measure for the prevalence of missed opportunities was calculated for each study. Seventy-nine studies were identified from 45 countries; 18 were population-based, 52 were health-service-based, and 9 were intervention trials. A median of 32% (range, 0–99%) of the children and women of childbearing age who were surveyed had missed opportunities during visits to the health services for immunization or other reasons. Missed opportunities were mainly due to failure to administer simultaneously all vaccines for which a child was eligible; false contraindications; health workers' practices, including not opening a multidose vaccine vial for a small number of persons to avoid vaccine wastage; and logistical problems. To eliminate missed opportunities for immunization, programmes should emphasize routine supervision and periodic in-service training of health workers which would ensure simultaneous immunizations, reinforce information about true contraindications, and improve health workers' practices.

Introduction

Based on information reported to the World Health Organization (WHO) as of September 1992, global immunization coverage for children by their first birthday was 85% for BCG (Bacille Calmette-Guérin) vaccine, 79% for three doses of diphtheria-pertussis-tetanus (DPT) vaccine, 81% for three doses of poliomyelitis vaccine, and 78% for measles vaccine. However, for pregnant women in developing countries, coverage was only 42% for two doses of tetanus toxoid. WHO estimates that in 1991 immunization prevented some 3 million deaths from measles, neonatal tetanus and pertussis, and some 530 000 cases of paralytic poliomyelitis. Additional efforts will be necessary to sustain this progress and to achieve, by the year 2000, the goal of fully immunizing 90% of the world's children by their first birthday. Perhaps the greatest challenge will be to raise the tetanus toxoid coverage of women to the same levels seen for children.

A direct approach to increasing immunization coverage is to provide immunization to all eligible persons at every opportunity. The strategy of immunizing at every opportunity has been recommended by the Global Advisory Group of the WHO Expanded Programme on Immunization (EPI) since 1983 (*1*). Immunizations should be offered at every contact point, including preventive and curative health services. Countries should review national immunization policy and remove excessive contraindications. Children suffering from malnutrition and minor illness are at particular risk for vaccine-preventable diseases and should be immunized.

An opportunity for immunization is missed when a person who is eligible for immunization and who has no contraindication to immunization visits a health service and does not receive all the needed vaccines.

Missed opportunities for immunization occur in two major settings: (1) during visits for immunization and other preventive services (e.g., growth monitoring, nutrition assessments, and oral rehydration training sessions) and (2) during visits for curative services. In both settings, eliminating missed opportunities will raise the overall immunization coverage

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Reprint No. **5414**

in a population, particularly when the availability and use of health services are high. When the availability and use of health services are low, immunizing at every health care contact is extremely important because the risk for vaccine-preventable diseases is likely to be high in these areas.

Since 1984, EPI has been promoting the use of a standard survey for assessing missed opportunities for immunization. In 1987, when the results from several surveys in developing countries indicated that the majority of children attending curative care facilities were missing opportunities to be immunized, the Global Advisory Group called for more surveys to investigate the magnitude of the problem among children and women of childbearing age and to identify strategies to reduce missed opportunities (*2*).

This review of 79 studies on missed opportunities from 45 countries provides information on their global magnitude, the demographic differences, and the reasons for failure to immunize during visits to the health services. Strategies to reduce missed opportunities are recommended, which emphasize the usefulness of periodic systematic monitoring to evaluate the quality of immunization programme performance at the health service level as well as progress towards reducing missed opportunities.

Methods

Criteria for inclusion of studies

Only studies that assessed missed opportunities for immunization in the EPI target groups (children and women of childbearing age) were included. We reviewed studies reported in the world literature on missed opportunities for immunization or failure to vaccinate and unpublished studies reported to WHO up to July 1991. The review considered only studies that defined a missed opportunity for immunization as any contact with a health service that did not result in an eligible child or woman receiving all the needed vaccines.

Classification by study design

Studies on missed opportunities for immunization were classified in two groups: observational surveys and intervention trials. Observational surveys measure missed opportunities through review of immunization or medical records or interviews with patients, parents or health care providers.

Observational surveys measure the magnitude and the importance of reasons for missed opportunities. They were further classified by the method used to select study participants as (1) population-based surveys and (2) health-service-based surveys. Representative population-based surveys can define the potential gain in immunization coverage achievable (in the total population) through eliminating missed opportunities. In practice, however, such surveys are difficult and expensive to conduct. Health-service-based surveys are more likely to be conducted. They offer the advantage of assessing reasons for missed opportunities in the setting where they occur; thus, specific operational recommendations can be made to the participating health facility.

Intervention trials measure the change in missed opportunities or immunization coverage before and after instituting an intervention to reduce missed opportunities. Intervention trials were further classified as (1) controlled trials with a comparison group in which no intervention was introduced during the study period; and (2) trials with historical controls that compared the occurrence of missed opportunities before the intervention to the occurrence in the same group after the intervention.

Calculating the prevalence of missed opportunities

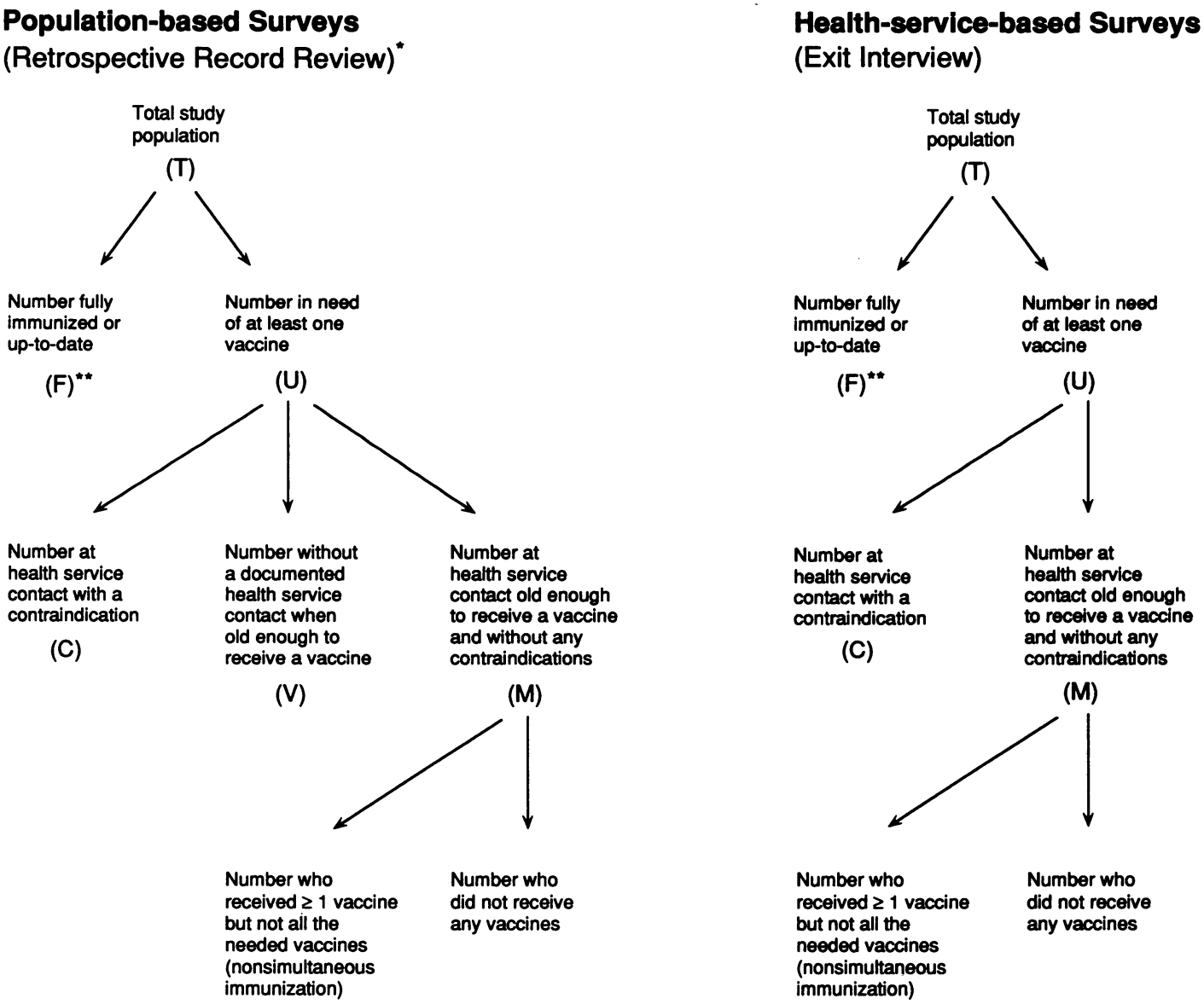
We calculated a standard summary statistic for the prevalence of missed opportunities for each study. When insufficient data were available from the study report, the authors were consulted for additional information. The prevalence of missed opportunities was calculated as the number of persons without a true contraindication to immunization who visited a health care centre and remained not fully immunized or up-to-date (for his/her age) according to the national immunization policy, divided by the total number of persons in the study population.

The method used to calculate the prevalence of missed opportunities is shown in Fig. 1. The total study population (T) was divided in two groups: those who were fully immunized or up-to-date for immunization for their age (F); and those who were not (U). These groups were based on the national immunization schedule in the country where the study was conducted. The number of children or women who missed at least one opportunity for immunization (M) was calculated by subtracting from U the number who had a true contraindication to immunization (C) and the number who were too young to be immunized (V). V was relevant only in population-based surveys or surveys where immunization cards or medical records were reviewed retrospectively.

The following equation was used to calculate the standard estimate of the prevalence of missed opportunities:

$$P1 = (U - V - C / F + U) \times 100, \text{ or}$$
$$P1 = (M / T) \times 100$$

Fig. 1. **Method for calculating missed opportunities** (see text for details).



* Includes health-service-based surveys that conducted retrospective record reviews.

** Up-to-date for age based on the immunization policy of individual countries.

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where $P1$ is the prevalence of persons in the study population who had at least one missed opportunity.

Calculating the inefficiency of health services

We also calculated the prevalence of missed opportunities for persons needing an immunization during the health visit. This statistic measures the inefficiency of the health service in immunizing eligible children and women. It is calculated by the following equation:

$$P2 = (U - V - C \,/\, U - V) \times 100, \text{ or}$$
$$P2 = (M \,/\, U - V) \times 100$$

where $P2$ is the proportion of eligible persons who had one or more missed opportunities.

Classification by reasons for missed opportunities

Reasons for missed opportunities were classified as (1) failure to administer vaccines simultaneously; (2) false contraindications to immunization; (3) negative

health worker attitudes; (4) logistical problems; and (5) refusal by the patient or family. The importance of each reason was measured as the overall prevalence of missed opportunities due to the specific reason. This information indicates the potential gain in coverage that could be achieved if that specific missed opportunity was eliminated.

Results

Types of studies

Seventy-nine studies on missed opportunities were identified from 45 countries.[a] Studies were conducted in each of the six WHO regions (Table 1). Worldwide, nearly one-quarter of all countries completed at least one study. Fifty-nine studies (75%) were conducted in developing countries and 20 (25%) in industrialized countries. Of the 79 missed opportunities studies, 52 (66%) were health-service-based studies, 18 (23%) were population-based studies, and nine (11%) were intervention trials.

Population-based observational surveys. Of the 79 studies reviewed, 18 (23%) were observational surveys that selected the study subjects by using a population-based approach. Thirteen population-based studies were conducted in 12 developing countries. Twelve of the 13 studies used EPI cluster sampling; one studied a village cohort. The EPI 30-cluster survey examines data on the home-based immunization card or child health record—specifically, the date of birth and the dates of immunization. The 30-cluster surveys in the Central African Republic,[b] Guinea (*3*), and Mozambique (*3, 4*) also assessed opportunities missed during health service visits, as the dates of these visits were recorded on the child health card. A total of more than 43 000 children and 22 000 women were studied in population-based surveys in developing countries.

Five population-based studies were conducted in two industrialized countries. Four studies used non-random samples of convenience; one used a random sample. Four studies were based on health records; one was based on parental interviews. In total, more than 1000 children were studied in industrialized countries.

Health-service-based observational surveys. Of the 79 studies that were reviewed, 52 (66%) were health-service-based observational surveys. Study subjects were selected from persons contacting health services: in 49 surveys the study subjects were outpatients, and in three surveys they were inpatients.

Forty health-service-based missed opportunity studies were conducted in 35 developing countries in all six WHO regions. The number of health facilities included in each survey differed considerably: 14 surveys (35%) included fewer than five health facilities; 15 (38%) included 5–19 facilities, and 11 (28%) assessed 20 or more health facilities. Of the 40 studies, 33 used the EPI exit interview protocol, 4 used record reviews, and 3 used hospital patient interviews. In total, more than 44 000 children and 52 000 women were studied at more than 500 health facilities in developing countries.

[a] The full list of studies and tables detailing results of each of these studies (unpublished document WHO/EPI/GEN/92.8) is available from the Expanded Programme on Immunization, World Health Organization, 1211 Geneva 27, Switzerland.

[b] **Directorate of Preventive Medicine, Ministry of Health, Central African Republic.** *Missed opportunities for vaccination: the potential impact on vaccination coverage of vaccinating at every health facility visit.* (Supplementary report for vaccine coverage survey, unpublished, May 1990).

Table 1: **Number of studies of missed opportunities for immunization in developing countries and industrialized countries, by WHO Region**

	Developing countries		Industrialized countries		Total	
WHO Region	No. of countries	No. of studies	No. of countries	No. of studies	No. of countries	No. of studies
Africa	15	19	–	–	15	19
Americas	12	15	1	14	13	29
E. Mediterranean	6	11	–	–	6	11
Europe	1	3	2	5	3	8
South-East Asia	6	10	–	–	6	10
Western Pacific	1	1	1	1	2	2
Global total	41	59	4	20	45	79

Twelve health-service-based studies were conducted in three industrialized countries located in three WHO regions. Two studies used exit interviews and 10 used record reviews. A total of more than 7000 children were studied at some 80 health facilities in industrialized countries.

Most developing countries assessed missed opportunities by using an EPI protocol. Parents and patients in the EPI target group were interviewed as they exited a health service and were queried about their child's or their own immunization history and the reason for the health visit. An interviewer determined the missed opportunity for immunization by using the reason for the health visit and the national policy on contraindications to immunization. Immunization history was obtained from immunization cards; when these were not available, information was based on parental or patient recall. Immunization cards were available for most of the children: a median of 84% (range, 48–100%) of the enrolled children had their cards. Cards were less frequently available for women, except for those attending antenatal clinics.

In countries where immunization records were kept in health care facilities, information was obtained from retrospective review of medical charts or immunization registers. The health-service-based method does not provide information on the magnitude of missed opportunities in the community unless the use of health services is high and a representative sample of all the health facilities in a community is surveyed. However, this method is useful for measuring the magnitude of missed opportunities at the health facility, identifying their causes, and designing specific recommendations to prevent future missed opportunities.

Intervention trials. Of the 79 missed opportunity studies reviewed, 9 (11%) were intervention trials. Eight trials used a health-service-based approach to select study subjects; one used a population-based approach. Only one intervention trial was a controlled trial; the others used historical controls.

Six intervention trials were conducted in developing countries; three trials were conducted in industrialized countries. The effect of an intervention was determined by measuring the change in the prevalence of missed opportunities or the change in immunization coverage before and after the intervention. Information on these outcomes was collected through interviews with the target group or health care provider, or through reviews of medical charts.

Prevalence of missed opportunities

Global. The 70 observational surveys from 44 countries were evaluated to determine the magnitude of missed opportunities for immunization. Opportunities for immunization were missed for a median of 32% (range, 0–99%) of the children and women of childbearing age who were surveyed. In 69 surveys, opportunities to immunize were missed. The only survey that failed to find missed opportunities was an exit interview survey in Zimbabwe, where the policy of vaccinating at every health contact was being successfully implemented for children at the two health facilities in the study (*5*). If opportunities to immunize had been taken in the specific populations and at the specific health services studied, immunization coverage would have increased by a median of 32%. Population-based studies suggest an increase by a median of 22% (range, 3–77%), while health-service-based studies indicate an increase by a median of 44% (range, 0–80%) among clinic attendees. Of children and women who were eligible for immunization at the health visit, a median of 67% (range, 0–100%) were not immunized. That is, a given health service contact was 67% inefficient in taking the opportunity to immunize eligible children and women.

Developing versus industrialized countries. Missed opportunities for immunizations were identified as an important problem both for developing and industrialized countries. Fifty-three observational studies were conducted among children in developing countries and 18 among children in industrialized countries. Studies included in this review showed that missed opportunities occurred more often among children in developing countries (median, 41%; range, 0–99%) than in industrialized countries (median, 15%; range, 3–55%). However, it is difficult to compare the findings from these two groups of countries since 14 (82%) of the 17 studies from industrialized countries were conducted in one country (USA), while no more than 3 studies were conducted in any one developing country. Moreover, lists of contraindications tend to be longer in industrialized countries than in developing countries. Since the formula we used to calculate missed opportunities excludes children with contraindications (based on national policy), this might lead to a lower prevalence of missed opportunities in industrialized countries.

Preventive versus curative health services. Ten surveys in 10 developing countries compared the prevalence of missed opportunities during preventive services with the prevalence during curative or other health services (Table 2). Some of these countries had national policies to immunize in curative services, others did not. Overall, opportunities for immunization were more likely to be missed in curative services than in preventive services. These

Table 2: **Prevalence of missed opportunities in preventive and curative health services in ten countries**

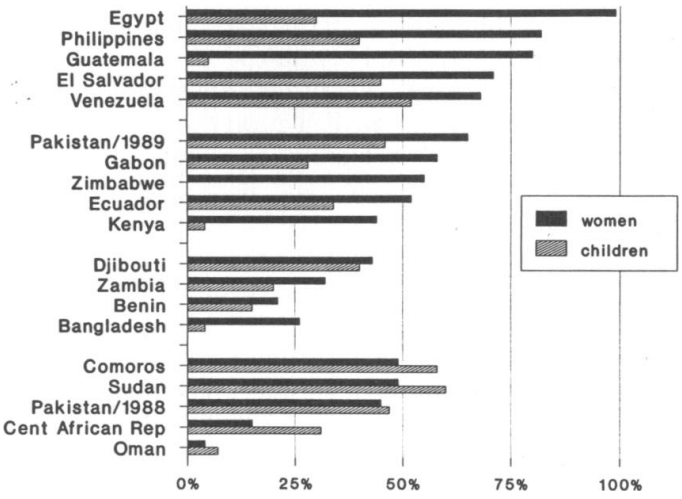
Country and reference	Study group	Prevalence of missed opportunities (%)	
		Preventive	Curative
Cameroon (*6*)	2–35 months	40	63
Central African Republic[a]	12–23 months	25	31
Comoros (*28*)	0–23 months	33	91
	Women	42	96
Ethiopia (*29*)	0–23 months	30	44
Gabon[b]	0–23 months	20	37
	Women	54	63
Guinea (*3*)	12–23 months	5	14
Mexico[c]	0–59 months	54	40
Mozambique (*3, 4*)	12–23 months	2	6
Puerto Rico (*30*)	2–59 months	51	53
Venezuela[d]	0–23 months	48	56
	Women	71	65
All countries			
Median (range):			
Children		32 (2–54)	42 (14–91)
Women		54 (42–71)	65 (63–95)

[a] See footnote *b* on page 552.
[b] See footnote *f* below.
[c] See footnote *d* below.
[d] See footnote *e* below.

surveys showed that many persons had visited health services at times when they were eligible for immunization and could have been immunized if immunizations were offered. In two surveys, in the Central African Republic[c] and in Mexico[d], missed opportunities were reported to occur more often during immunization services than during other health services, indicating a problem with the routine immunization delivery system.

Routine screening in health facilities was found to be important in ensuring that eligible persons were immunized during visits for services other than immunization. For example, in surveys conducted in the Cameroon (*6*) and Venezuela[e], persons who attended curative services missed opportunities only when there was no routine screening to determine their immunization status. A study in Sudan demonstrated the importance of using screening at curative services (*7*). "Never immunized" children were identified at curative services but were less likely to be seen at preventive services.

Fig. 2. **Prevalence of missed opportunities among women (aged 15–44 years) and children (aged 0–23 months) in 19 surveys.**



An alternative use for a missed opportunities survey is to provide information on what improvements in immunization coverage could be expected by extending the number of days that immunizations are routinely offered. Studies were conducted for this purpose in Burundi and Gabon. In Gabon,[f] for children and women, a 2- to 3-fold increase in missed opportunities was found on the days when immunizations were not scheduled. In Burundi,[g] missed opportunities for children were lowest in facilities that immunized at every health contact (15%), compared with facilities that immunized every day but not at every contact (21%), or facilities that immunized fewer than four days per week (30%).

Women versus children. Of the 59 surveys of children in developing countries, 19 also surveyed women of childbearing age (Fig. 2). In 14 of these studies, women were found to have many times more missed opportunities than children. Only five studies found the prevalence of missed opportunities to be lower for women than for children. These data indicate that coverage of women of childbearing age with tetanus toxoid could be greatly improved by taking advantage of contact with health services to immunize women.

[c] See footnote *b*, page 552.

[d] **Romero, M.G. et al.** [*Missed opportunities for immunization of under-5-year-olds in Mexico.*] (Unpublished report, in Spanish, 1990).

[e] **Vellozi, C. et al.** *Vaccine coverage and missed opportunities of vaccination in Caracas, Venezuela.* (Unpublished report, 1989).

[f] Evaluation du Programme Elargi de Vaccination: Gabon, novembre 1989.

[g] **Tharcienne, N.** *Impact de la politique de vacciner les enfants à tout contact.* Université du Burundi, Faculté de Médecine, 1990.

Table 3: **Prevalence of missed opportunities, by vaccine**

Country and reference	Percentage of immunizations needed but not administered			
	BCG	DPT	OPV	Measles
Bolivia (*31*)	35	28	25	52
Colombia (*14*)	86	64	59	74
Ecuador (*31*)	29	30	33	58
Guatemala (*32*)	NA	48	47	20
Honduras (*31*)	68	36	31	49
Mexico[a]	83	80	74	84
Nicaragua (*33*)	65	69	54	74
Nigeria[b]	8	10	11	19
Peru (*31*)	NA	48	47	36
Puerto Rico (*30*)	NA	42	42	68
United Kingdom (*17*)	NA	27[c]	37	20
Venezuela (*31*)	8	42	32	30
Zambia[d]	18	76	84	72
All countries				
Median	35	42	42	52
(range)	(8–86)	(10–80)	(11–84)	(19–84)

[a] See footnote *d* on page 554.
[b] **Federal Ministry of Health, Nigeria.** *Nigeria national coverage survey, preliminary report, April 1991.*
[c] Includes persons with true contraindications.
[d] **Szegedi, E.** *EPI progress report, January–July 1990, Zambia.*

Vaccine-specific missed opportunities. Missed opportunities were measured for specific vaccines in 13 surveys in 13 countries; ten (77%) were from the Region of the Americas (Table 3). Although there were considerable differences among countries, surveys in seven countries demonstrated that an opportunity to immunize with measles vaccine or BCG was missed more often than an opportunity to immunize with DPT or oral poliomyelitis vaccine (OPV). This difference may relate to the fact that these vaccines are given only once. Compared with DPT and OPV, it is more likely that only one child or a few children will require immunization with BCG or measles vaccine during a single immunization session; therefore, the fear of vaccine wastage may be higher (see below, negative health worker attitudes).

Reasons for missed opportunities

In general, the broad categories of reasons why immunizations were not given during a health visit were similar for developing and industrialized countries, although the relative importance of each reason within the broad categories differed. Developing and industrialized countries reported problems with inefficient scheduling of immunization services and long waiting times (*8, 9*). Vaccine shortage was reported as a problem in some developing countries but not in industrialized countries. In developing countries, the fear among health workers about wasting vaccine if they open a multidose vaccine vial for one child was identified as an important reason for missed opportunities. In the surveys on missed opportunities that were reviewed, parental refusal to immunize children was a minor reason for missed opportunities; however, in industrialized countries, it may be more of a problem (*10*). Similarly, false contraindications may be more of a problem in industrialized countries (*10–13*).

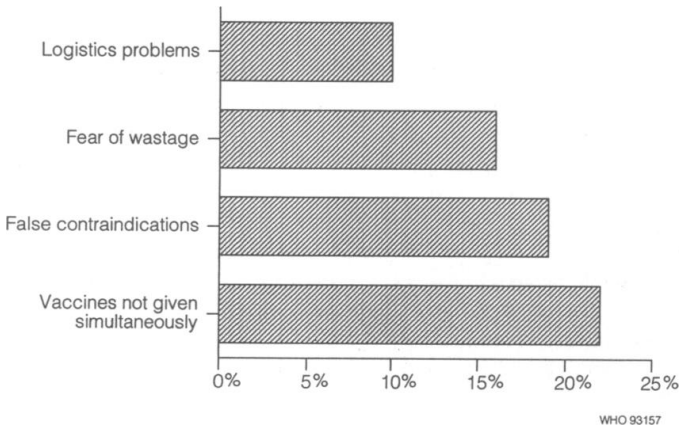
Reasons for missed opportunities were classified into five categories; details of this analysis are reported below and summarized in Fig. 3.

Failure to administer imunizations simultaneously. Failure to administer immunizations simultaneously was one of the major reasons given in eight surveys where this was specifically assessed. In these surveys, a median of 22% (range, 2–38%) of persons missed opportunities because immunizations were not administered simultaneously. This measurement may be an underestimate because many surveys classified failure to administer vaccines simultaneously as a logistical problem.

False contraindications. Twenty-seven surveys assessed the role of false contraindications for immunizations and 24 (89%) identified this as a problem. In these surveys, a median of 19% (range, 6–65%) of persons missed an opportunity because of false contraindications to immunization.

Negative health worker attitudes. Negative attitudes of health workers, including fear of wasting the vaccine, and not offering, thinking about, or screening for immunization, were assessed in 11 surveys and all found it to be one of the major reasons for missed opportunities. In these surveys, a median of 16% (range, 1–26%) of persons missed opportunities because of negative health worker attitudes.

Fig. 3. **Four major reasons why immunization opportunities were missed (expressed as percentage of median prevalence).**



Logistical problems. Logistical problems with immunization delivery (e.g., vaccine shortage, poor clinic organization, and inefficient clinic scheduling) were assessed in 11 surveys. This reason was found to be important in all 11 surveys. The median prevalence of missed opportunities for children and women due to logistical problems was 10% (range, 1–24%).

Parental refusal. In nine surveys, the refusal of immunizations by patients or their families was assessed. In general, lack of parental acceptance of immunization was not an important reason for missed opportunities. Missed opportunities due to patient or parental refusals occurred in a median of 3% (range, 2–11%) of persons.

Strategies to eliminate missed opportunities

Strategies tested in intervention trials

Nine intervention trials were conducted in eight countries. After implementation of one or more interventions, each of the nine trials demonstrated a reduction in missed opportunities or an increase in immunization coverage, although only three studies showed statistically significant changes. Of the nine trials, missed opportunities were reduced by 8–69% and immunization coverage was increased by 10–145%.

The only trial designed to determine whether the observed change in missed opportunities was due specifically to an intervention was a controlled trial conducted in Venezuela in 1989.[h] Nine clinics were included: in six clinics, letters and posters explaining the true contraindications to immunization were distributed; in three of these clinics, health records of children in need of immunizations were marked with a special stamp; in three control clinics no interventions were used. Surveys on missed opportunities conducted before and 1 month after these interventions found statistically significant declines in the prevalence of missed oportunities at *all* nine clinics. These results probably reflect the response of persons in the control clinics to an unplanned extra intervention, the distribution of immunization buttons.

A study in El Salvador[i] demonstrated significant reductions in missed opportunities for children (69%), women of childbearing age (14%), and pregnant women (44%) after the institution of multiple interventions. Specifically these were (1) providing pre-intervention survey results to health care providers whose clinics were surveyed, (2) emphasizing the issue of false contraindications during in-service training, (3) stressing the role of health workers as future health facility directors, and (4) notifying health workers about plans to conduct a repeat survey to measure the progress towards reducing missed opportunities.

A third trial that demonstrated a statistically significant reduction in missed opportunities was conducted in the State of Georgia, USA, during 1987–90 (V. Dietz, personal communication, 1992). Interventions included annual reviews of missed opportunities and immunization coverage; an award system to motivate health workers; and the provision of immunization services in federal nutrition assistance programmes serving public clinics. These interventions led to an 85% increase in immunization coverage in public clinics and an 80% decrease in the prevalence of missed opportunities.

The remaining trials implemented a variety of interventions. In Colombia, health workers and parents were notified about the need to assess immunizations at every health care visit and missed opportunities were reduced by 37% (*14*). In Djibouti[j] the interventions included offering immunizations every day, opening multidose vials of vaccine (even for one child), and screening all women and children who visited the health facility. In Nigeria, one clinic introduced an express lane for immunization services, so that children no longer had to wait to be seen by a physician before getting immunized (*8*). In Sudan, an intervention introduced at curative clinics was screening and immunizing either before or after the physician's consultation (*15*). In Fife, United Kingdom, general physicians were sent letters encouraging them to administer measles vaccine and the coverage increased by 27% (*16*). In Manchester, United Kingdom, children admitted to a hospital paediatric ward were screened for immunization status and immunized if eligible (*17*).

Zimbabwe EPI experience. In 1987, a survey of missed opportunities conducted in two clinics in Zimbabwe found no missed opportunities for children aged 3–23 months (*5*). The Zimbabwe EPI actively promotes a policy of immunizing eligible persons at every contact with a health facility. To effectively use opportunities in paediatric clinics, a

[h] **Vellozi, C. et al.** *An intervention trial for missed opportunities of vaccination in Caracas, Venezuela.* Unpublished report, 1989.

[i] **Hernandez Pimentel, J.F.** [Study of missed opportunities for immunization, Western Health Region, El Salvador.] Unpublished report, 1989 (in Spanish).

[j] **Said Salah.** *Rapport des enquêtes des occasions de vaccinations manquées.* Service d'Hygiène et Epidémiologie, Ministère de la Santé Publique et des Affaires Sociales, République de Djibouti. Document 348/SHE/89, mai 1989.

nurse screens every ill child for immunization status and vaccinates all eligible children, even before the physician's consultation. The cost of this strategy is reported as US$ 0.02–0.04 per patient per day.

Conclusions and recommendations

A number of potentially effective strategies to reduce missed opportunities have been recommended by the Global Advisory Group and tested in studies conducted in both developing and industrialized countries. Immunization programme managers should identify specific reasons for missed opportunities in their programmes, select the most appropriate strategy, and monitor the effect of the strategy in reducing missed opportunities.

Based on the reasons identified in this global review of missed opportunities, the following recommendations are relevant for immunization programmes in all countries.

(1) *Use missed opportunities surveys routinely*

Studies reported above have shown that the assessment of missed opportunities is a useful managerial tool, as well as a method suited to health services research. EPI has developed a module for EPI mid-level managers to assess the causes of missed opportunities and to determine effective strategies for their elimination. The module, entitled "Identify missed opportunities" has been prepared to serve district and provincial staff as a supervisory and evaluation tool.

Further studies at the national, district, and provincial levels may provide guidance for policy decisions. Studies may be planned to determine the specific age groups, geographic areas, and immunization services in which immunizations are most often missed. The importance of specific reasons for missed opportunities should be assessed, including gaps in health workers' knowledge, attitudes, and practice.

(2) *Screen and immunize at every contact*

This review found that missed opportunities for immunization affect both children and women of childbearing age and occur in both preventive and curative health services. Many persons eligible for immunization have contact with health services and could be immunized if vaccines were offered. Furthermore, the increased risk for children of contracting measles in health facilities has been documented in both developing and industrialized countries, underscoring the importance of protecting them through immunization at every health service contact (*18, 19*). Routine screening for immunization status should be carried out on all children and women of childbearing age who visit health services for any reason. The timing for screening in the patient-flow process should be tailored to the health service. Intervention trials indicated that screening and immunizing before or after the physician's consultation were equally effective. Ideally, eligible persons should be immunized immediately, or at least referred for immunization. National immunization policy may need to be revised or fully enforced so as to focus on screening for immunization at every health service contact.

To facilitate screening for immunization status at every health visit, immunization cards should be used for both children and women of childbearing age. Mothers should be reminded to bring their child's and their own immunization or health record whenever they have contact with a health service.

(3) *Administer vaccines simultaneously*

In this study, failure to administer immunizations simultaneously was found to be a major cause of missed opportunities. Administering vaccines simultaneously, when indicated, should be the rule. The vaccines currently used in the EPI (BCG, OPV, DPT and measles vaccine) can all be given simultaneously. These vaccines may also be given at the same visit when yellow fever vaccine and hepatitis B vaccine are administered. In-service training and periodic supervisory visits should assist in reducing this type of missed opportunity.

Whether opportunities for simultaneous immunization are being taken can be readily assessed in immunization coverage surveys that use COSAS, software available from EPI for analysis using a personal computer. WHO estimates that more than 100 coverage surveys are analysed each year with COSAS.

(4) *Emphasize true contraindications*

False contraindications to immunization were found to be a major cause of missed opportunities. To avoid this type of missed opportunity, health workers should have in-service training and be reminded periodically through posters and supervisory visits about the true contraindications to immunization. The fact that EPI vaccines have few true contraindications should be emphasized. Countries should review and, if necessary, redefine their policy on contraindications.

In general, children who have illnesses that do not require hospitalization should be immunized. Therefore, children suffering from malnutrition, low-grade fever, mild respiratory infection, diarrhoea, and other minor illnesses *should* be immunized. The immunization status of hospitalized children should be assessed and they should receive appropriate immunizations before discharge. If possible, they

should be immunized against measles on admission because of the high risk of hospital-acquired measles (*20*).

True contraindications include not giving a second or third dose of DPT vaccine to a child who had a severe adverse reaction to the previous dose. In this situation, the pertussis component should be omitted and only the diphtheria and tetanus immunizations are given.

Unimmunized persons with clinical (symptomatic) HIV infection in countries where the EPI target diseases remain serious risks should not receive BCG, but should receive the other vaccines. In general, live vaccines are not given to immunocompromised persons, but in developing countries the risk of measles and poliomyelitis in unimmunized infants is high, and the risk from these vaccines, even in the presence of symptomatic HIV infection, appears to be low (*21*).

A precaution should be taken when administering OPV to a child who has diarrhoea. OPV should be given, but to ensure full protection, a dose given to a child with diarrhoea should not be counted as part of the series. The child should be given another dose at the first available opportunity.

Immunizations are just as effective in sick children as in healthy ones, and there is no increased risk of side-effects in sick children (*20*). However, one small study recently published in the USA reported that measles seroconversion rates after a dose of measles-mumps-rubella (MMR) vaccine were 79% for children with a mild upper respiratory infection, compared with 99% for well children (*22*). This study has not had any impact on global policy to immunize sick children for the following reasons. First, the study is not consistent with previously reported studies from developing countries (*23, 24*). Second, the study findings are unusual, since a lower seroconversion rate was found only for measles and not for mumps or rubella (*25*). Finally, it should be emphasized that the measles immunity conferred by giving a single dose (79%) of measles vaccine was much higher than not giving any vaccine (0%).

Concerns about immunizing women with tetanus toxoid during early pregnancy have not been justified. There is no convincing evidence of risk to the fetus from immunizing pregnant women with tetanus toxoid (*26*).

(5) *Provide continuing education on immunization*

In-service education is essential and immunization updates should be provided at least annually to all health workers (curative and preventive). Information on immunization can readily be included in meetings of medical and nursing associations. In countries where the private sector provides immunizations, guidelines and training should be made available. Inclusion of EPI training materials in medical, paramedical, public health, and nursing school curricula may be an effective method of positively influencing the attitudes of health workers early in their training.

(6) *Reduce fear of vaccine wastage*

The EPI policy of opening a multidose vial, even for one eligible child or woman, should be emphasized again and again. The availability of smaller multidose vials may encourage health workers to follow this practice. Today most vaccines for developing countries are purchased in 20-dose vials. At the end of an immunization session, all open vaccine vials, whether used or only partly used, must be discarded. EPI training materials indicate that wastage rates of 25% are to be expected. Nevertheless, this study found that the health workers' concern about wasting vaccines if they open a multidose vial for one child or woman was an important reason for missed opportunities.

In 1991 these findings led to a series of studies of vaccine wastage in different countries (*27*), which showed markedly higher wastage rates than expected. When immunization sessions were held one or more times a week, wastage rates were as high as 40–60% for OPV and DPT, and 80–90% for BCG. In this situation, changing from a 20-dose vial to a 10-dose vial reduced vaccine wastage by as much as 20–40%.

In the absence of other information, programmes should choose to use 10-dose vials for DPT, OPV, and tetanus toxoid, and 5-dose vials for measles when immunization sessions are held more frequently than once a week. In most cases, the savings from the reduced wastage will be greater than any increase in purchase and delivery cost per dose when smaller vials are used. The availability of a smaller multidose vial may encourage health workers to open a multidose vaccine vial, even for one child.

Acknowledgements

We are grateful to the EPI staff in the WHO Regional Offices, especially J.-M. Olive, AMRO, for sharing information and ideas. We thank N. Begg, F. Cutts, M. Deming, V. Dietz, F. Gasse, J. Gindler, M. Grabowsky, and B. Moriniere for updating us on their studies, and K. Bergstrom, J. Cheyne, F. Cutts, S. Hadler, R.H. Henderson, W. Orenstein, D. Salisbury, and R. Steinglass for helpful comments and advice.

Contributions of the Rockefeller Foundation and the United Nations Development Programme to the WHO Expanded Programme on Immunization were used to fund the development and testing of the missed opportunities survey method. Many immunization staff in the field tested this method, often under difficult conditions.

Résumé

Etude des occasions manquées de vaccination dans les pays en développement et dans les pays industrialisés

Bien que la couverture vaccinale ait été considérablement augmentée dans le monde entier depuis la mise en œuvre du Programme élargi de vaccination en 1974, les efforts doivent être poursuivis tant dans les pays en développement que dans les pays industrialisés pour atteindre d'ici l'an 2000 l'objectif d'une vaccination complète de 90% des enfants du monde. Pour améliorer la couverture vaccinale, une approche directe consiste à réduire les occasions manquées de vaccination dans les services de soins de santé existants.

Afin de déterminer l'ampleur et les raisons des occasions manquées de vaccination chez les enfants et les femmes en âge de procréer, les rapports publiés dans le monde entier sur cette question, ainsi que les travaux non publiés communiqués à l'OMS jusqu'en juillet 1991 ont été examinés. Les études sur les occasions manquées de vaccination ont été classées en fonction de leur conception — enquêtes d'observation au niveau de la population, enquêtes d'observation au niveau des services de santé, et essais d'intervention. Une mesure type de la prévalence des occasions manquées a été calculée pour chaque étude. Cette mesure donne des indications sur le gain potentiel en termes de couverture si ces occasions manquées étaient éliminées.

Les études sur les occasions manquées de vaccination ont fait l'objet de 79 rapports répertoriés dans 45 pays en développement et pays industrialisés; 18 de ces études portaient sur l'ensemble de la population, 52 sur les services de santé et 9 consistaient en essais d'intervention. Des études ont été faites dans chacune des six Régions de l'OMS. A l'échelle mondiale, près d'un quart de l'ensemble des pays ont réalisé au moins une étude, et les trois quarts des études ont été faites dans des pays en développement. Une médiane de 32% (intervalle 0–99%) des enfants et des femmes en âge de procréer qui avaient été enquêtés ont manqué une occasion de vaccination au cours de leurs visites dans un service de santé pour une vaccination ou pour d'autres raisons. D'après les études portant sur la population, si ces occasions manquées étaient éliminées, la couverture vaccinale pourrait être augmentée d'une médiane de 22% (intervalle 3–77%); d'après les études portant sur les services de santé, la couverture vaccinale chez les consultants des dispensaires pourrait être augmentée d'une médiane de 44% (intervalle 0–80%). Les principales raisons des occasions manquées de vaccination étaient: 1) impossibilité d'administrer simultanément tous les vaccins qu'un enfant était susceptible de recevoir (médiane 22%; intervalle 2–38%); 2) fausses contre-indications à la vaccination (médiane 19%; intervalle 6–65%); 3) pratiques des agents de santé (médiane 16%; intervalle 1–26%), notamment refus d'ouvrir un flacon multidoses de vaccin pour un petit nombre de personnes afin d'éviter de gaspiller le vaccin; 4) problèmes logistiques, par exemple manque de vaccin, mauvaise organisation du dispensaire, planification inefficace (médiane 10%; intervalle, 1–40%). Pour améliorer cette situation, les programmes devront insister sur la supervision en routine et sur la formation en cours d'emploi des agents de santé afin de faire en sorte que la vaccination simultanée soit pratiquée, de renforcer l'information sur les véritables contre-indications, et d'améliorer les pratiques des agents de santé. Il est possible d'encourager les agents de santé à ouvrir un flacon multidoses de vaccin, même pour un seul enfant ou une seule femme, en fournissant des flacons de 10 doses. Il semble que l'utilisation en routine d'un flacon de 10 doses pour le DTC et le VPO soit plus économique que celle d'un flacon de 20 doses, car il est maintenant fréquent de devoir procéder à de petites séances de vaccination portant sur moins de 10 personnes.

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Vaccine 32 (2014) 6870–6879

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

A systematic literature review of missed opportunities for immunization in low- and middle-income countries

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ARTICLE INFO

Article history:
Received 24 August 2014
Received in revised form 18 October 2014
Accepted 21 October 2014
Available online 4 November 2014

Keywords:
Immunization
Missed opportunity
Vaccine
Vaccine hesitancy
Systematic review
Meta-analysis

ABSTRACT

Background: Missed opportunities for immunization (MOIs) may contribute to low coverage in diverse settings, including developing countries.
Methods: We conducted a systematic literature review on MOIs among children and women of childbearing age from 1991 to the present in low- and middle-income countries. We searched multiple databases and the references of retrieved articles. Meta-analysis provided a pooled prevalence estimate and both univariate and multivariate meta-regression analysis was done to explore heterogeneity of results across studies.
Results: We found 61 data points from 45 studies involving 41,310 participants. Of the 45 studies, 41 involved children and 10 involved women. The pooled MOI prevalence was 32.2% (95% CI: 26.8–37.7) among children – with no change during the study period – and 46.9% (95% CI: 29.7–64.0%) among women of child-bearing age. The prevalence varied by region and study methodology but these two variables together accounted for only 12% of study heterogeneity. Among 352 identified reasons for MOIs, the most common categories were health care practices, false contraindications, logistic issues related to vaccines, and organizational limitations, which did not vary by time or geographic region.
Conclusions: MOI prevalence was high in low- and middle-income settings but the large number of identified reasons precludes standardized solutions.

1. Introduction

After the Global Advisory Group of the World Health Organization (WHO) recommended the strategy of immunizing at every opportunity in 1983, protocols were developed for evaluating the magnitude and risk factors for missed opportunities for immunization (MOI) by WHO [1]. It defined a missed opportunity as an occasion when a person eligible for immunization and with no valid contraindication visits a health service facility and does not receive all recommended vaccines. Following the publication of a systematic review on missed opportunities during 1993 [2], the goal was set to achieve full immunization of 90% of the world's children by 2000. This goal has not been achieved as of 2013, and one of the major contributors is MOIs [3].

The objective of our study was to perform a systematic literature review to assess the prevalence of missed immunization opportunities in low- and middle-income countries since publication of the last summary review during 1993. We focused on children and women of child-bearing age – as these are the target groups for publicly funded immunization programs in the evaluated countries – and assessed the importance of temporal and geographic variations.

2. Materials and methods

2.1. Database search

Two authors (SS and NM), conducted the database search and data extraction. We included searches of the following: PubMed, Cochrane, Popline, WHO regional databases (LILACS: Latin American and Caribbean; IMSEAR: Index Medicus of South East Asian

Abbreviations: AJOL, The African Journal Online; IMEMR, Index Medicus Eastern Mediterranean region; IMSEAR, Index Medicus of South East Asian Region; LILACS, Latin American and Caribbean; MOI, missed opportunity for immunization; PAHO, Pan American Health Organization; UNICEF, United Nations International Children's Emergency Fund; WHO, World Health Organization; WPRIM, Western Pacific Region Index Medicus.

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http://dx.doi.org/10.1016/j.vaccine.2014.10.063
0264-410X/

Region; PAHO: Pan American Health Organization; WPRIM; Western Pacific Region Index Medicus; IMEMR: Index Medicus Eastern Mediterranean region), the African Journal Online (AJOL), and Google Scholar. Databases requiring paid access (EMBASE, CINAHL etc.) were not included because of budget constraints; despite this, after consultation with the WHO librarian, the authors considered that the included databases were likely to have identified all or the great majority of relevant manuscripts.

Our goal was to include immunization terms combined with practices, services and type of study. Our search terms included "immunization" OR "vaccination" (or any of numerous synonyms) in combination with "Health Knowledge, Attitudes, Practice" OR "Attitude of Health Personnel" OR "Immunization/trends" OR "Immunization/utilization" OR "Immunization/physiology" OR "Vaccination/psychology" OR "Vaccination/trends" OR "Vaccination/utilization" OR "Preventive Health Services/trends" OR "Health Services/trends" OR ("Health Services/utilization" AND "Epidemiologic Studies") OR "Follow-Up Studies" OR "Health Surveys" OR "Data Collection". For PubMed, MeSH (Medical Sub-headings) was used to help expand the search. These terms were then combined with the names of individual low- and middle-income countries. Additional manuscripts in French papers were searched on Google using the terms ([Opportunité] AND [manquée/perdue] AND [vaccination/immunization]) OR (Perte AND opportunité AND vaccination).

2.2. Inclusion criteria and selection process

We included studies that measured the magnitude or described the reasons for missed opportunities in children (0–18 years) or woman of childbearing age in low- or middle-income countries (as defined by the World Bank during 2013) after 1991. Only studies in English, Spanish, French and Portuguese were included based on staff translation capacity.

Following pilot testing of the selection form, two independent reviewers reviewed in a stepwise fashion the title, abstract, and full text using Distiller Software (Fig. 1). Discrepancies were resolved through consensus. The references of all included manuscripts were searched for additional manuscripts. As indicated in Fig. 1, we had three ancillary searches. The African Journal Online database was searched for the terms "missed" AND "immunization" AND "opportunities"; this led to 53 results, of which three manuscripts were included after title abstract and full text screening. The Google search for French references yielded 30 results, of which four manuscripts eventually were included. Lastly, a secondary PubMed search using the term "missed immunization opportunities" led to 307 results and seven included manuscripts.

2.3. Quantitative data extraction

Of 59 [4–62] identified manuscripts, 45 [4–48] were included in quantitative analysis. These 45 studies included data on the number of persons with MOI as well as the total population under study eligible for vaccination (N), regardless of study methodology. Study participants were considered to have a MOI if they visited a healthcare facility, were not up-to-date on recommended immunizations, and did not receive recommended immunizations irrespective of the number of visits. The total population (N) eligible for vaccination equaled the sum of persons who were fully or partially vaccinated, those who had false contraindications for vaccination, and those with missed opportunities. Some manuscripts provided more than one data point, for example data for multiple countries (one report from South America had information on 10 countries) or for both women and children. For these cases, we included each data point separately in analysis (Table 1).

2.4. Qualitative data extraction

Qualitative data included reporting source, definition of missed opportunities, reasons for MOIs, and limits and quality of data.

2.5. Statistical analysis

All analyses were carried out in Stata version 12. Prevalence was calculated directly from manuscripts as a ratio of the number of children or women with MOIs divided by the total eligible population and the standard error calculated. Pooled estimates were calculated during meta-analysis using the *metan* command [63] in Stata on the prevalence and standard error. Heterogeneity was explored statistically using *Cochrane Q* and *I2* values, a statistic that quantifies the degree of inconsistency across studies in a meta-analysis on a scale ranging from 0 to 100%. A random effects model was used for weighting because of a high level of heterogeneity between studies. Results were stratified by WHO region, year of the study (time trend), methodology, and age group of children.

Eight variables in the dataset were reported commonly enough to be evaluated as potential covariates. Bivariate regression analysis was performed to establish the association between each of these variables and the prevalence estimate. Variables associated with missed opportunity prevalence with a p-value <0.05 on bivariate analysis were included in a meta-regression analysis [64]. Meta-regression was performed with the "metareg" command using prevalence as the outcome variable. All analyses were done separately for women and children.

2.6. Quality assessment

No standard method exists for assessing data quality in descriptive reports. Consequently, we developed the following methodological quality scoring system based on four variables:

- Location: health center based but no details given as to the nature of the site = 0; retrospective community-based = 1; health center based and details provided = 2.
- Methodology: recall/no immunization cards = 0; immunization cards = 1; exit interviews/health center records = 2.
- Definition of missed opportunity used in the study: non-WHO definition = 1; WHO definition = 2.
- Sample size: ≤500 = 0, 501–1000 = 1, >1000 = 2.

The study authors developed the scoring system and information for all variables was extracted from the manuscripts themselves. The scoring system was developed as a means of standardizing bias assessment and to account for the lack of explicit bias assessment in most of the included studies. We considered that community-based household surveys due to their retrospective nature were more susceptible to recall bias than studies conducted in health centers. With respect to study methodology, we considered that exit interviews combined with health center records had the least bias in assessing immunization status. With respect to MOI definition, we considered that use of the WHO definition was less biased than an ad hoc definition, although we recognize no empiric data support this decision. These first three variables were used as measures of study validity, while the final variable was used as a measure of study precision. To calculate the total score, we summed values for these four variables.

3. Results

We identified 59 studies from 31 countries and 6 WHO regions (Supplemental Table 1). Of these, 45 studies (containing 61 data

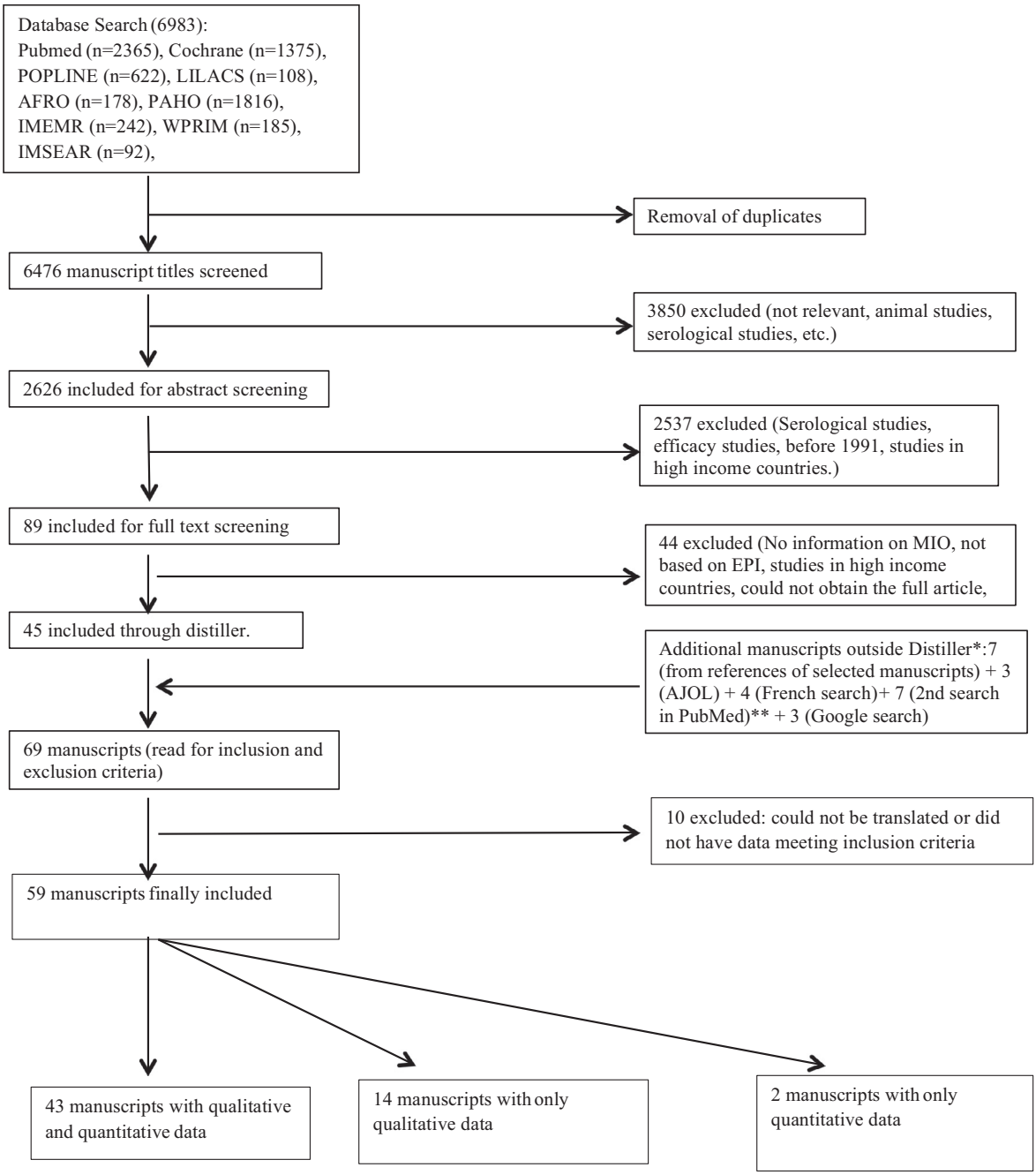

Fig. 1. Flow chart representing results of the systematic review.

Table 1
The prevalence of missed opportunities for immunization by vaccine type.

Country	Setting	BCG (%)	DPT (%)	Measles (%)	OPV (%)
India [45]	Population based	37.1	31.2	–	–
Ghana [22]	Not specified	–	–	75	–
South Africa [20]	Mixed[a]	–	–	15.7	–
Papua New Guinea [46]	Tertiary hospital	15	36	26	36
South Africa [17]	Population based	5.1	35.8	35.8	35.8
Guinea [16]	Population based	8	18	15	18
South Africa [15]	Mixed	–	–	16.2	–
Brazil [34]	Tertiary hospital	0.4	19	6.4	13.4
India [43]	Population based	–	–	15.3	–
Philippines [47]	Tertiary hospital	0.3	4.9	4.9	3
Nigeria [25]	Tertiary hospital	5	48	70	46.7

[a] Mixed refers to mix of various types of hospitals (primary, secondary and tertiary care centers).

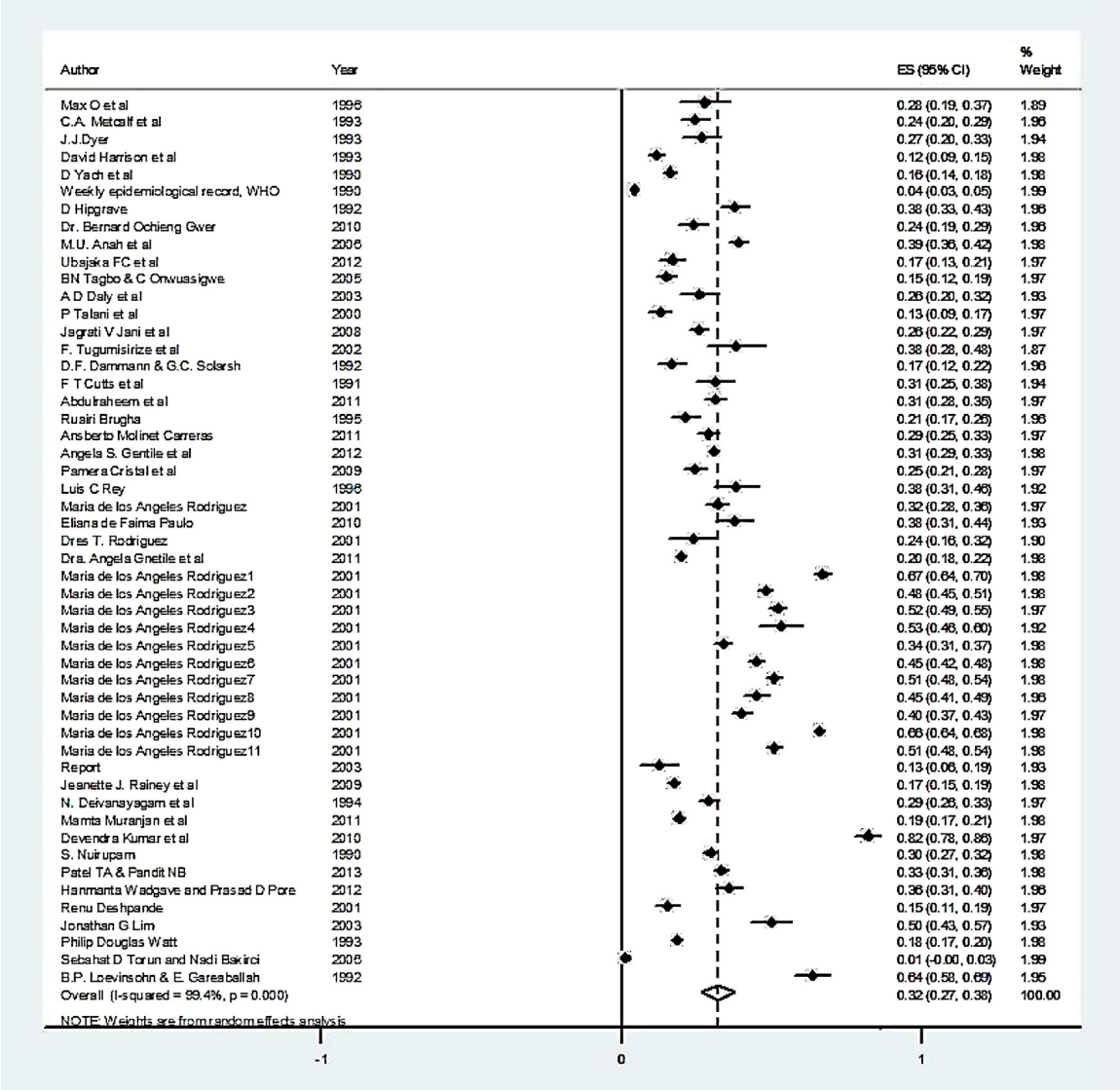

Fig. 2. Forest plot showing the pooled prevalence estimates of missed opportunities for immunization among children.

points) had data available for quantitative and 57 for qualitative analysis (Supplemental Table 2). Of the 61 data points available for quantitative analysis, 48 had data from health services-based studies (including 46 based on exit interview and 2 on hospital record surveys) while 13 were from population based studies (including 4 based on vaccination card review and 9 based on card review plus interviews). The majority of studies reported data for children (51 out of 61 data points used for quantitative analysis) and for this reason most analyses were performed only for studies with data on children.

3.1. Quantitative results in children

For the 51 data points available for children, the prevalence of MOIs ranged from 1.3% in a study in Turkey [4] to 82% in a study in India [5]. The pooled MOI prevalence estimate was 32.2% (26.8–37.7) (Fig. 2). MOI prevalence was modestly higher in the Americas than in Africa and Southeast Asia (Fig. 3). Most of the studies in the African, American, and Southeast Asian regions measured MOI prevalence using exit interviews (Fig. 4), following WHO recommendations.

We did not identify any increase or decrease in MOIs over the study period (Fig. 5). To control for potential confounding by unmeasured factors that varied by country, we evaluated three individual countries from three different WHO regions that had at least six data points. While we found a slight increase in prevalence in South Africa [10,15,17,19–21] and India [5,8,41–45] and a decrease in Brazil [31,34,35,39], none of these changes were statistically significant.

Of 26 studies with information available on setting, 19 [5,9,11,12,14,15,18,20,22–24,31,34,38,39,42,44,46,47] measured missed opportunities only in a curative setting, 4 studies only in a preventive setting [13,33,35,45] and 3 in both settings [8,10,25]. The pooled prevalence estimated in the curative setting was 33.4% (95% CI: 23.8–43.0) and in the preventive setting was 17.8% (95% CI: 9.4–26.1). When considering only the three studies that measured data in both settings, no difference in pooled prevalence was seen.

Eleven studies [15–17,20,22,25,34,43,45–47] reported MOI prevalence by vaccine type (Table 1). Of these, six studies included all of the following vaccines: BCG, DPT, measles and OPV. With the exception of one study in India, BCG (recommended for use during the newborn period) had the lowest prevalence while patterns for other vaccines varied by study.

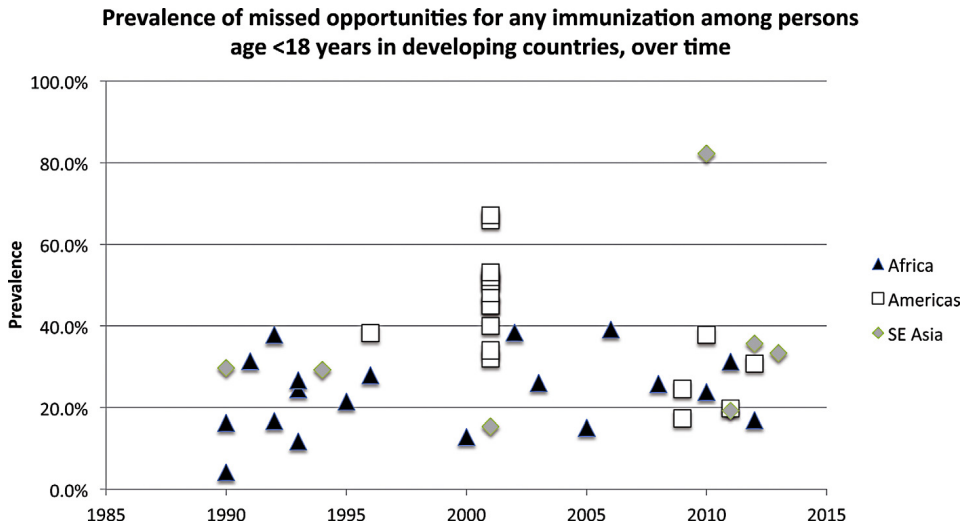

Fig. 3. Prevalence of missed opportunities for any immunization among persons age 0–18 years in developing countries, over time.

3.2. Risk factor analysis in children

During bivariate analysis, there was an association ($p < 0.05$) between MOI prevalence and region of study, methodology, and age group of the population. Age group categories, however, were not mutually exclusive (that is, studies using differing and overlapping age group categories) making it impossible to include this variable in a multivariate analysis. In the final meta-regression, both study methodology ($p = 0.089$) and study region ($p = 0.048$) were associated with MOI prevalence to approximately the same degree. The final model R-square was 12%. A second model was created with year of study entered as a dichotomous variable based on pre-2005 and post-2005, but this did not change results.

3.3. Women of reproductive age

Ten studies provided 10 data points for women of reproductive age. The pooled MOI prevalence was 46.9% (CI: 29.7–64.0%) and ranged from 11.6% in a study in Ethiopia [6] to 88% [7] in a study in Swaziland. Six data points derived from the African region [6,7,18,23,29,30], two from the American region [31,40] and one study each from the Southeast Asian [42] and European regions [48]. Of the 10 data points, seven were collected using the exit interview methodology.

3.4. Reasons for missed opportunities for immunization

We included 57 studies in the analysis of reasons for missed opportunities. These studies reported 352 reasons for children and women of reproductive age. These reasons were categorized as related to service providers, the parents, and the immunization system (Table 2). Among children, most reported reasons were categorized as related to service providers and parents. Lack of availability of vaccines and other logistic problems were less commonly reported. Economic barriers were rarely reported.

Of the 10 articles with information on women of childbearing age, four had information exclusively on women (specifically, for tetanus toxoid vaccine). The reasons mainly revolved around healthcare practices of the providers and logistic problems.

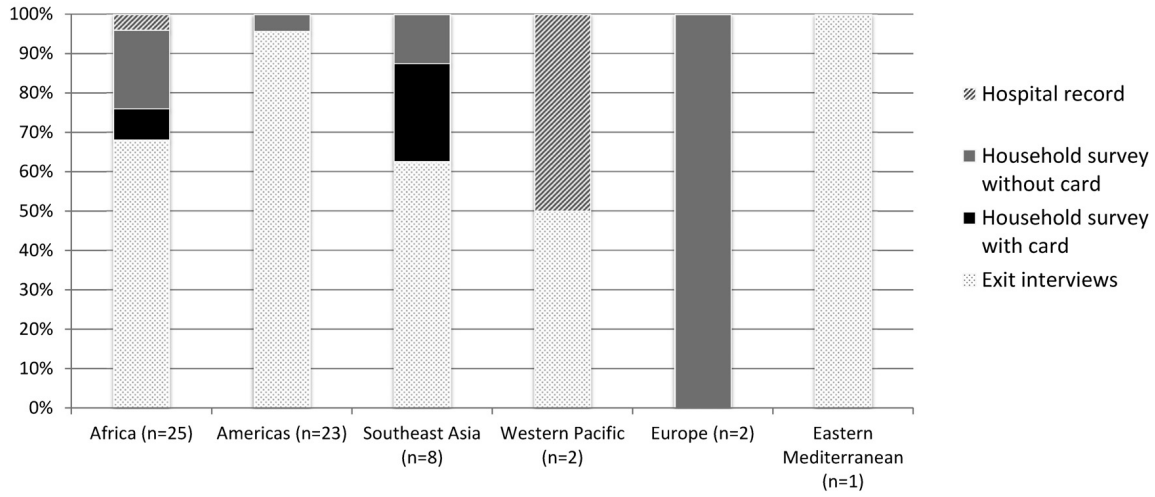

Fig. 4. Methodology used to assess missed opportunities for immunization for six World Health Organization Regions.

Table 2
Reasons for missed opportunities for immunization among children and women of reproductive age-group.

I. Children	*317*
A. Practices	75
1. Health care providers (HCP)	59
Immunization cards not reviewed	13
Immunization history not reviewed	9
HCP reluctant to open vaccine vial	8
Immunization not offered	7
Delays	4
Referral to clinics or other services	3
Lack of interaction and communication	2
Negative attitude of HCP	2
No administration of vaccines simultaneously	2
No advice to vaccinate	2
Practices (not detailed)	2
Negative attitude from the HCP	1
Not following the new policy	1
Patients discharged	1
Reminder not given by the health staff	1
Wrong immunization history	1
2. Parents	16
Immunization cards not available	10
Children did not report to the immunization staff	1
Forgetfulness in bringing the subjects to the vaccine providers	1
Maternal causes	1
No administration of vaccines simultaneously	1
Not following the new policy	1
Unavailable immunization card	1
B. Perceived contraindications	65
1. Health care providers	18
Not further detailed	6
Concurrent illness	5
Concurrent treatment for illness	2
Difficult birth	1
Low birth weight	1
Preterm birth	1
Underweight	1
Previous history of vaccine reaction	1
2. Contraindications (parents)	47
Concurrent sickness not otherwise specified	34
Concurrent infection	6
Not otherwise specified	4
Preterm birth	3
Concurrent treatment for illness	2
Under nutrition	1
C. Immunization session organization	56
Lack of time to perform immunizations given other provider duties	9
Lack of health staff	8
Long waiting time	7
Days designed for immunization limited	7
Need to separate preventive and curative services	4
Distance to center too far	3
Lack of orientation toward immunization	3
Poor communication about immunization	2
No schedule	2
Vaccination rooms not accessible	2
Lack of information	1
Lack of interaction	1
Lack of organization	1
Lack of physical space to perform immunizations	1
No days designated for immunization	1
Quality of health services	1
Schedules not communicated	1
Vaccination rooms far from consultation rooms	1
D. Logistics	33
Lack of vaccines (out of stock, not accessible to curative services)	21
Logistical problems not otherwise specified	6
Closed room	1
Cold chain failures, poor stock control	1
Irregular vaccine supply	1
Lack of adequate material	1
Lack of electricity	1
Lack of water	1

Table 2 (*Continued*)

E. Awareness, beliefs and knowledge	28
1. Awareness: health care provider	4
Lack of health care provider knowledge and awareness	3
Vaccination not seen as necessary	1
2. Awareness: parents	7
Vaccination not seen as necessary	2
Lack of awareness	1
Lack of information on vaccine availability	1
Lack of parental awareness	1
Many children	1
Vaccination not seen as necessary for older children	1
3. Beliefs: health care providers	2
Beliefs about side effects	1
Fears	1
4. Beliefs: parents	5
Concern about vaccine safety	1
Cultural plus religious reasons	1
Cultural reasons	1
Fears (unspecified)	1
Fears about side effects	1
5. Knowledge: health care providers	2
Knowledge on cold chain management	1
About prescription of vaccinations	1
6. Knowledge: parents	8
Lack of knowledge (not specified)	3
Lack of knowledge about expanded program on immunization	2
Calendars not known	2
Days designated for immunization not known	1
F. Attitudes	18
1. Health care providers	4
Negative attitude	1
Refusal	1
Refusal to deliver multiple doses	1
Vaccination not seen necessary	1
2. Parents	14
Refusal	5
Negative attitude of parents	3
Forgetfulness	2
Delays	1
Refusal of several doses	1
Stress	1
Vaccination not seen necessary	1
G. Economic barriers	8
Lack of money	5
Lack of transportation	2
Lost daily wages	1
H. Determinants	28
Other	6
Older child age	6
Lower maternal education	6
Place of delivery	3
Maternal unemployment	2
Older maternal age	1
Young maternal age	1
Child's death	1
Lower paternal education	1
Marital status of mothers	1
Women of reproductive age	*35*
A. Practices	8
1. Health care providers	7
Immunization cards not reviewed	2
Immunization history not reviewed	2
Immunization not offered	1
No advice to vaccinate	1
Referrals	1
2. Parents/recipients	1
Immunization cards not available	1
B. Attitudes	7
1. Health care providers	5

Table 2 (*Continued*)

Immunization not seen as a priority	1
Lack of motivation	3
Negative attitude of health care provider	1
2. Parents/recipients	2
Carelessness	1
Fear of being vaccinated during pregnancy	1
C. Awareness, beliefs and knowledge	7
1. Awareness: health care providers	1
Lack of awareness/knowledge	1
2. Awareness: parents/recipients	1
Lack of awareness/knowledge	1
3. Beliefs: health care providers	1
Vaccination not seen necessary	1
4. Knowledge: health care providers	2
Lack of knowledge	1
Schedules for immunization not known	1
5. Knowledge: parents/recipients	2
Lack of knowledge (purpose, schedules)	1
Lack of knowledge about number of doses	1
D. Organization	7
Days designed for immunization limited	2
Lack of information	2
Lack of time	2
Lack of communication	1
Lack of productivity	1
E. Contraindications	2
Concern for the safety of women during early pregnancy	1
Menstruation	1
F. Logistics	2
Inefficient immunization record keeping system	1
Lack of vaccines	1
G. Economic barriers	1
Lack of money	1
H. Determinants	1
Pregnant and no previous children or only one child	1
Total	352

There were 173 reasons for MOIs cited before 2005 and 179 after 2005 (total = 352). Reasons remained fairly constant over time except that before 2005, 27% ($n = 173$) of identified reasons were related to health care provider practices whereas after 2005, this number decreased to 11% ($n = 179$). In the African region, 30% of cited reasons were categorized as perceived contraindications whereas in the Americas, this reason accounted for 11%. Among all cited reasons in a curative setting, 24% were related to health care provider practices; among all cited reasons in a preventive setting, were related to parental perceived contraindications.

3.5. Quality assessment

Of the 61 data points, the mean quality assessment score was 6.0 out of a possible 8: three data points (5%) came from studies with a score of 2 or 3; 15 (23%) had a score of 4 or 5; 32 (52%) a score of 6 or 7; and 11 (18%) a score of 8. The mean score for children was 6.1 (range 2–8) and for women of reproductive age 5.2 (range 3–7). The mean score for data points in Africa was 5.4 (range 4–8) compared to 6.8 (range 4–8) for the Americas and 6.0 (range 2–8) for Southeast Asia. Three of our data assessment score categories evaluated bias; when considering only these three categories, the mean score was 5.3 out of a possible 6 (range, 3–6). The remaining score category measured precision; the mean score for this single category was 0.7 out of a possible 2.

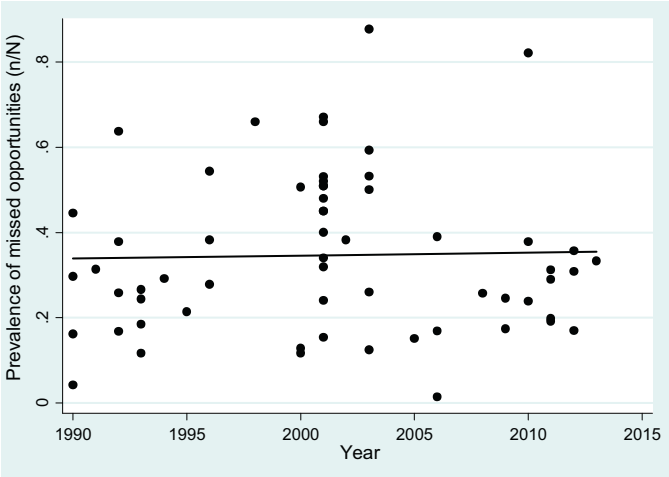

Fig. 5. Scatter plot showing trend in the prevalence of missed opportunities for immunization over time since 1991 (line shows fitted value).

4. Discussion

During 1993, WHO released its first report on missed immunization opportunities globally, which identified a median prevalence of 41% (range; 0–99%) in developing countries [2]. Several strategies then were adopted to address this issue. In 2005, WHO and UNICEF together published the Global Immunization Vision and Strategy (GIVS) for the decade 2006–2015 [65]. According to this, there was an increase in quantities of WHO prequalified vaccines offered to UNICEF after 2003. However, assessment of individual vaccine procurement by UNICEF shows a varying picture. Since 2003, the DTP procurement per year has been steadily falling and in 2013, there was a reported shortage of 5 million doses which was requested to be supplied [66]. By contrast the procurement of *Haemophilus influenzae* type b conjugate and hepatitis B vaccines from WHO increased since 2003 [67]. Also, by mid-2005, 53 countries, mostly in Asia and Africa, had begun implementing the RED (Reaching Every District) strategy, which takes the district as its primary focus and aims to improve equity in access to immunization by targeting difficult-to-reach populations [65]. This strategy focused on training for good immunization practices, timely collection of data on vaccine coverage and other vaccine-related activities (logistics, supply, and surveillance), proper supervision of immunization health workers, and involvement of communities in the planning and delivery of immunization services.

Given these substantial efforts, it would have been reasonable to expect a substantial decrease in the number of missed opportunities. However, the median prevalence for missed opportunities among children in our review was 32%, which is only modestly lower than the 1993 estimates. Moreover, no improvement could be documented over the 22-year time horizon of the current study. While studies from 2005 and later showed some decrease compared to earlier studies, methodological differences make conclusions difficult. This point is emphasized by the evaluation of individual countries, which show no evidence of declining MOI prevalence.

Additionally, efforts to increase immunization coverage do not equate with efforts to reduce MOIs because these are in part separate issues. For example, at the extreme, an area with high curative care use combined with high but delayed coverage delivered entirely in preventive settings could lead to both high MOI prevalence and high coverage.

We found higher MOI prevalence in the Americas than Africa, despite the much greater level of economic advancement and immunization infrastructure in the former area. The main reasons

for missed opportunities were immunization services practices, organization, and logistical barriers; all of these in theory should drive prevalence higher in more disadvantaged African settings. Methodological issues could explain some of the observed difference. For example, studies in the Americas were more likely to use exit interviews; additionally, studies only included persons who presented to health care facilities and thus by definition had enough resources for health care access. However, it may also be that missed opportunities do not occur primarily for economic reasons in lower income settings where most persons receive vaccines free of charge through national immunization programs, even if other cost barriers to attending an immunization clinic exist. Consistent with this observation, individual financial constraints were rarely reported as a cause of MOIs.

While studies evaluated missed opportunities in preventive and curative services, only three studies simultaneously evaluated both, and these studies found no difference by setting [8–10]. Nevertheless, we found different categories of reasons in the two settings, suggesting that intervention strategies will need to be tailored. Additionally, while the prevalence of missed opportunities may be similar in each setting, the bulk of immunizations are delivered in preventive settings and the barriers to implementing more complete immunization should be less in settings designed for this purpose. Finally, if immunization delivery in preventive settings functioned perfectly at all levels, no reason would exist to deliver immunization in curative settings. Consequently, we think the bulk of intervention efforts should focus on immunization clinics.

While some reasons for missed opportunities were more common than others, no single reason, or even category of reason, accounted for more than 25% of the total. This indicates that efforts to decrease missed opportunities must be multifaceted. Efforts to increase card retention would be useful and some strategies have been successful [68]; alternatively, new technologies such as rapid detection of biomarkers may identify children in need of vaccination [69,70]. Prefilled syringes or single-dose vials can overcome reluctance to open multi-dose vials [71]. Social messaging and provider training may address perceived contraindications. However, in settings with high mortality, not vaccinating children with serious acute or chronic illness may do more good for the immunization program as a whole even if it does not serve the interests of the individual child; this is because deaths temporally but not causally related to immunization nevertheless may be perceived as causally related by parents or community members. Opportunities exist to design better immunization systems that facilitate immunization delivery both for providers and recipients. Examples include SMS messaging [72], improved outreach strategies [73], and better organization of immunization sessions with adequate staff, time, and immunization rooms. For eligible countries, the GAVI Alliance financing window for health system strengthening could be used to support some of these activities. While we did not identify large differences in categories of reasons between Africa and Asia, it is likely that specific issues will be heavily influenced by the local cultural context, especially with regards to attitudes and beliefs.

While much overlap existed in reasons for missed opportunities between the current review and that conducted during 1993 [2], differences also were found. In particular, the 1993 review found that a substantial proportion of missed opportunities resulted from failure to administer vaccines simultaneously or patient refusal while more recent studies rarely reported these reasons. Polyvalent vaccines could have contributed to a decline in the former, as could better training of health care providers. Vaccine refusal or hesitancy has been attributed to various factors and the reasons range from individual or personal beliefs to contextual factors like wars to vaccine specific adverse events. WHO has addressed vaccine refusal over the last decade, which might have resulted in studies infrequently citing patient refusal as a reason for MOI in our study [74]. Regardless, the decline in two major reasons for missed opportunities combined with little evidence of an overall decrease in missed opportunities prevalence emphasizes the dynamic nature of this phenomenon. Consequently, decreasing missed opportunities is likely to require ongoing monitoring for new causes, particularly with the advent of social media, which can greatly amplify the speed and penetration of concerns related to immunization.

The main limitation of the current review was the highly varied methodology. Identified studies varied in the definition of missed opportunities, sample size, method of measurement, population, location, and other features. The lack of a gold standard methodology for conducting such studies also made it difficult to assess the degree to which methodology impacted differences between studies. Many studies reported reasons for missed opportunities as isolated events, whereas it is likely that in most cases missed opportunities resulted from a dynamic web of interrelated processes including system integration, communication between actors, culturally based concepts of immunization, differing health and economic priorities, and other issues. We identified a relatively small number of studies, which prevented more robust comparisons by region, age, and study methodology. We do not know the representativeness of studies we evaluated for other regions; in particular, studies tend to be conducted in urban centers or countries with a richer history of research.

Studies also were subject to a variety of biases. Selection bias occurred in the selection of the study population and the selection of cases within this population. For the former, studies frequently used populations that were easily accessible even if they were not representative of the underlying population. Across the studies, the age group of the children that were studied varied considerably. None of the groups were mutually exclusive. Cases selected for inclusion varied by the definition used. While most studies used the WHO definition (55 out of 61 data points), others used their own definitions. For example, according to the standard MOI case definition, persons who refused vaccination should be excluded, but this was not done consistently across studies.

Information bias occurred in studies using different methods to ascertain immunization receipt including immunization cards or other written records as well as verbal histories. Within studies relying on verbal histories, different persons provided this information, which may have influenced data accuracy.

Lastly, despite our efforts to identify all relevant papers, a systematic review is inherently an imperfect process due to issues such as differences in language use, something that likely is accentuated with a non-standardized outcome such as missed opportunities for immunization.

5. Conclusions and recommendations

Our data leads to several conclusions and recommendations. Implementation of standardized methodology would facilitate greatly comparison over space and time. Standardization should include the study setting, population, and interview methodology; the case definition should address explicitly issues such as whether patient refusal is considered part of the definition; and valid versus perceived contraindications should be identified. The Pan American Health Organization released an implementation manual [75] which gave a detailed definition of an eligible child, vaccines to be considered, vaccination schedule, study design, sample size and study population. The manual might be improved through inclusion of information on valid contraindications and

a clear position on whether patient refusal is considered a MOI. Finally, to be effective the manual needs to be implemented widely.

More studies are needed to determine if specific vaccines or presentation characteristics lead to more or fewer missed opportunities. As public immunization programs expand outside of infancy and pregnancy, studies will be needed on new target groups such as toddlers, adolescents, and the elderly. Because of the great variety of reasons contributing to missed opportunities, immunization professionals should identify interventions that could address various issues simultaneously. Additionally, identification of a reported reason for a missed opportunity does not necessarily mean that this reason was a necessary condition and thus that appropriate intervention would have eliminated the missed opportunity; to make this link, a need exists for well-designed intervention research including randomized trials [8,11].

Conflict of interest

All authors worked for AMP at the time of the study; AMP receives unrestricted support from Sanofi Pasteur and grant specific support from Crucell, GSK, Merck, Novartis, Pfizer and Sanofi Pasteur.

Acknowledgments

AMP: Audrey Gavard-Lonchey for project management. WHO: Alina Ximena Riveros Balta, Ana Maria Henao Restrepo and Thomas Allen for assistance with study design and literature searches.

The World Health Organization (Grant no. 2013/3422963-0) – Geneva provided funding for this research.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.10.063.

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Establishing a 2nd year of life health child visits as a platform for vaccination and other health interventions (2YL)

Concept note

In 1974, the World Health Organization (WHO) launched the Expanded Programme on Immunization (EPI) with a goal to protect every child against six specific vaccine-preventable diseases: diphtheria, pertussis, tetanus, measles, poliomyelitis, and tuberculosis. Initially, immunization schedules focused on vaccines against these diseases given in the first year of life. Subsequently, WHO has substantially increased the number of recommended vaccines to be given by all immunization programmes to include vaccines against hepatitis B, *Haemophilus influenzae b*, pneumococcal disease, rotavirus, rubella, and Human Papillomavirus. However, many immunization programmes still perceive childhood immunization as a health intervention only for children <1 year old and do not offer vaccinations to children over 1 year of age even if the child was never vaccinated. Even when policies are in place to allow vaccination of children over 1 year of age, this often does not translate to a change in practices.

In line with this, there are multiple benefits to establishing a strong platform for immunization and other interventions in the 2nd year of life:

1) **Provides an additional routine contact for vaccination in 2YL: primary doses, booster doses and second doses.** Booster doses of routine immunizations such as for DTP are increasingly recognized of public health importance. In addition, a second dose of measles containing vaccine (MCV2) is recommended in some settings. Although some countries offer MCV2 at school entry ages, most offer MCV2 during the second year of life. For some newer vaccines such as pneumococcus vaccine, and meningitis A vaccine, one schedule option includes a routine dose in the second year of life. There are also multiple vaccines in development such as vaccines for malaria and dengue fever that will likely be recommended for children over 1 year of age. Having an established platform for immunization in the 2nd year of life will increase the potential uptake of these vaccines once introduced.

2) **Achieve higher coverage of vaccines offered in the first year of life through catch-up vaccination**. A strong platform in the 2nd year of life provides an important opportunity to provide missed vaccines to children and to improve overall coverage. By expanding vaccination services to the 2nd year of life, a child will no longer be limited to a 3-month window for receipt of MCV1; this change will positively impact the achievement of the measles elimination goals. Other missed doses in infancy should also be given at this time.

3) **Create opportunities to integrate with other health interventions**. Immunization systems are increasingly integrated with other health interventions with the intent of maximizing public health impact with limited resources. The 2nd year of life is an opportunity to further integrate immunizations with other health interventions such as Vitamin A supplementation, nutrition, growth monitoring, and deworming.

WHO is developing guidance to countries to establish a “healthy child visit” in the second year of life to achieve the benefits mentioned above. To inform this guidance, in-depth reviews of the introduction of a routine measles second dose in Zambia and Senegal are in the process to being completed. Further inputs to

the guidance will include a landscape analysis and literature review conducted by UNICEF, and a long term evaluation project of the measles second dose introduction by CDC in Ghana. Finally, grey literature and personal experience and anecdotes from national programmes on their experience to date will help inform the guidance document. The intent is to then implement this guidance in four further countries in 2017 to fine-tune it.

The following major issues emerging in this discussion include:

1. **Unexpected complexity**: While many national programmes assumed the introduction of a measles second dose (MCV2) and creating a visit in the second year of life as straightforward, the reality has shown that it brings with it a lot of complexity, in some cases complexity never encountered before by EPI programmes. Successful scheduling and implementation of a 2nd year of life healthy child visit requires better planning and implementation support than anticipated.

2. **Required definition, clarification and guidance**: Further work is required to better define and clarify key concepts, including
    - what constitutes a 2YL visit (given that many countries have a primary dose vaccination visit at 12 months);
    - how missed doses before 12 months impact understanding of the need for doses in the 2YL (eg. if a child missed their MCV1 in the first year of life, health workers may be confused on how the dose given in the second year of life should be given and called;
    - how to conceptualize the notion of a "Fully Immunized Child", both within a country and when aggregating data for many countries;
    - at what age MCV1 doses should be measured, and if this should be standardized globally (given that countries schedule the first dose at 9 months or at 12 months, but currently are counted at 12 months and 24 months respectively);.

3. **Recording and reporting documents and practices**: Currently, monitoring systems often lack the capability to record, report, and monitor vaccinations in age groups beyond infancy and are therefore of limited use to measure the impact of a 2YL platform. Furthermore, tally sheets, summary sheets and monitoring tools may send "messages" that direct behaviour inappropriately. For example, observations from multiple settings suggest that a form disallowing the entry of MCV1 doses above 12 months may direct health workers not to give such a dose even when it is national policy. Likewise, excluding untimely doses from performance measures may provide perverse incentives to not administer those vaccinations, or record them in the wrong age range. Forms should be adapted to assure that they provide adequate resolution to provide programme direction without becoming too burdensome or drive behaviour against stated policy;

4. Definition of a **package of interventions** and the complexity in introduces in terms of programmatic coordination, revisions to policies and standards, and implications at health facility level for health worker workload, patient flow, and data management across health interventions;

5. **Implementation research**: The implementation of a new healthy child visit (as opposed to the introduction of a new vaccine) should be investigated through implementation research projects. Specific research questions should be included to differentiate between supply and demand factors and their relative role in the establishment of a 2YL and its successful implementation;

6. **Development of guidance for the establishment of a 2nd year of life healthy child visit:** Using the case studies, demonstration projects, landscape analyses and literature reviews to develop guidelines for national programmes for the establishment of s 2nd year of life healthy child visit.

7. **Support to implementation of a 2nd year of life healthy child visit:** In four countries, both those that intend introducing a routine measles second dose, and those not intending to introduce a measles second dose, provide technical and implementation support to the establishment of a 2nd year of life healthy child visit.

8. **Development of information, education, and communication (IEC) materials and processes to support their use.** Possibly in the context of the proposed demonstration projects or independent of these projects, IEC materials should be developed and refined to inform parents of the importance of vaccinating in the 2nd year of life and to guide health care workers on how to catch-up children behind in their immunization doses (catch-up schedules, minimum interval between doses, etc.). Opportunities to bring these tools into regular use should also be identified to ensure that they are brought into standard practice.

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BACKGROUND PAPER ON DENGUE VACCINES

PREPARED BY THE SAGE WORKING GROUP ON DENGUE VACCINES AND WHO SECRETARIAT

17 MARCH 2016

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1. EXECUTIVE SUMMARY

Dengue is the most extensively spread mosquito-borne virus. In the last 60 years the incidence of cases of clinical dengue reported to WHO has increased 30-fold, with a much increased geographic range and expansion from urban to rural settings. Vector control is an important component of a comprehensive dengue control strategy; however, as a single strategy, it has been difficult to demonstrate its effectiveness in reducing the human dengue burden and large scale trials are lacking. The world requires a safe and efficacious dengue vaccine.

The first dengue vaccine, CYD-TDV (Dengvaxia®) has now been licensed by several dengue-endemic countries in Asia and Latin America for use in 9-45 or 9-60 year-olds, and it is under regulatory review in several others. To support licensure, CYD-TDV was evaluated in two parallel Phase 3 clinical trials, known as CYD14 and CYD15. CYD14 was conducted in 5 countries in Asia (Indonesia, Malaysia, Philippines, Thailand, and Vietnam), with 10,275 participants aged 2-14 years at first vaccination. CYD15 was conducted in 5 countries in Latin America (Brazil, Colombia, Honduras, Mexico, and Puerto Rico (US)), with 20,869 participants aged 9-16 years at first vaccination. In the trials the vaccine was evaluated with a 3-dose schedule given on at 0/6/12 months.

In the trials, the vaccine showed partial protection against virologically-confirmed dengue in the two years after the first dose, during which time there was active surveillance for symptomatic dengue of any severity. Vaccine efficacy over 25 months from the first dose among 9-16 year-olds, pooled from both CYD14 and CYD15 (post-hoc analysis), was 65.6% (95%CI 60.7-69.9). Protection was evident following the first dose and showed little variation up to one year following the third dose. Vaccine efficacy in these first 25 months varied by infecting serotype (higher protection against DENV 3 and 4), age (higher protection in 9-16 year age group), and severity (higher protection against hospitalized and severe dengue). Most notably, vaccine efficacy was high among participants 9 years of age or older who were seropositive (i.e., had previous exposure to dengue) at baseline (81.9%, 95%CI 67.2-90.0), and lower among participants who were seronegative at baseline (52.5%, 95%CI 5.9-76.1). Serostatus and age were highly correlated in the population studied. The seroprevalence among participants 9 years of age or older was approximately 80% in both Phase 3 trials.

After these first 25 months of follow up, participants were monitored for dengue disease on the basis of hospitalizations only. In most age groups, there was continued partial protection through the ongoing 5th year of follow up. In those first vaccinated at ages 2-5 years in Asia, a statistically significant increased risk of hospitalized dengue was seen in vaccine recipients in the third year after the first dose. The increased risk diminished and was not statistically significantly elevated compared to controls in the 4th and 5th years. Considering follow up from the beginning of the trial to date, there is an excess of cases of hospitalized dengue among vaccinated children in the 2-5 year age group, which is not statistically significant. No other safety signals have been identified in any age group. Aggregated across all efficacy trials with over 4 years of follow up, there was evidence that CYD-TDV was partially protective against hospitalized dengue in those aged older than 5 years at first vaccination. These findings led to the current indication, the intention being to set it conservatively, starting at 9 years of age.

Mathematical modelling suggests that in high[1] transmission settings, the introduction of CYD-TDV in early adolescence through routine immunization could reduce dengue hospitalizations by 10-30% over the period of 30 years, representing a substantial public health benefit. The modelling predicted that the vaccine would be less beneficial in low transmission settings, due to the higher proportion of seronegative individuals, among whom the vaccine may have limited protective effect.

[1] For the purposes of this document, transmission settings are defined by seroprevalence at age 9 years: very low ~10%, low ~30%, moderate ~50%, high ~70%, very high ~90%.

Given the predicted variable impact of the vaccine according to transmission intensity, the modelling indicated that it is a better use of resources to target vaccination to areas with higher transmission. As with many mosquito-borne diseases, dengue transmission is highly heterogeneous and may vary substantially across small geographical areas, suggesting a potential benefit to subnational, targeted introduction.

While there are currently no data to indicate an increased risk of hospitalization due to dengue in vaccine recipients in the indicated age range of 9-45 years, *there is a theoretical possibility that vaccination may be ineffective or may even increase that risk in those who are seronegative at the time of first vaccination*. Targeted studies, in parallel to vaccine implementation, are needed to address these questions, otherwise it will remain a controversial issue and could compromise public confidence in the vaccine program.

Proposed Recommendations

Countries should consider introduction of CYD-TDV in geographic settings (national or subnational) with high dengue transmission, i.e. seroprevalence of approximately 70% or greater in the age group targeted for vaccination but not below 50%.[2]

Where possible, assessment of dengue transmission intensity should be supported by geographically relevant seroprevalence studies. Seroprevalence estimates should guide decision-making and introduction at subnational levels while noting that these are not precise indicators. Work is needed to identify routinely collected epidemiologic indicators that can be used to infer likely seroprevalence.

Decisions about introduction require careful assessment at the country level, including consideration of local priorities, subnational dengue epidemiology, predicted impact and cost-effectiveness with country-specific hospitalization rates and costs, as well as affordability and budget impact. Vaccination should be considered as an integrated strategy together with well-executed and sustained vector control and the best evidence-based clinical care for all patients with dengue.

CYD-TDV is recommended as a three dose series given 6 months apart. While protection has been documented after administration of the first dose, completion of the three-dose scheduled is recommended to assure the protection demonstrated in the 5-year period of trial follow up so far. Should a vaccine dose be delayed for any reason, it is not necessary to restart the course and the next dose in the series should be administered. Because of the duration of the vaccine schedule and to enable better vaccine monitoring, countries should have systems in place for tracking vaccination.

The target age for routine vaccination should be defined by each country based on an assessment of dengue endemicity and programmatic feasibility of targeting particular ages. The age to target to optimize impact likely varies by transmission setting.[3] Although only immunogenicity (not vaccine efficacy) has been studied in clinical trials of 17-45 year-olds, in principle these age groups could be targeted for vaccination. At this stage, insufficient data are available to permit a recommendation for use above the age of 45 years. No vaccination is recommended under age 9 years due to the potential safety concern signalled in children aged 2-5 years of age in the Phase 3 trial.

[2] Mathematical modelling suggests optimal public health and economic impact in these transmission settings. Seroprevalence of 50% was at the lower end of the range of participants in Phase 3 trial sites. The overall seroprevalence in 9-16 year-old trial participants in the Phase 3 studies was approximately 80%. Modelling cautions against CYD-TDV use in lower transmission settings in early adolescence.

[3] Mathematical modelling found 9 years of age was optimal only in very high transmission settings (seroprevalence of 90% in that age group). In other settings with moderate to high transmission, vaccination between 11 and 13 years is predicted to maximize impact, although the variability in impact with age of vaccination was not great.

Risk of dengue hospitalization has been monitored for up to 4 years post-dose 3 in the Phase 3 trials. In the age group currently part of the indication (9-16 years), there is evidence of decreasing protection against dengue hospitalization over this time period. Ongoing follow up from the Phase 3 trials will provide information on the duration of protection, and it is possible that booster doses may be necessary to maintain protection. Currently there is no recommendation for a 4th dose.

Co-administration is not recommended until data are available on the safety and immunogenicity of CYD-TDV when co-administered with other age-appropriate vaccines.

CYD-TDV should be introduced as part of a routine immunization program in appropriate settings. Catch-up campaigns targeting priority age groups defined by local epidemiology can be considered for a greater immediate impact. While adding age cohorts will give progressively better disease control, mathematical modelling of catch-up campaigns in 10-17 year-olds does not suggest a significant impact on dengue transmission (i.e. herd immunity). Future research will study a possible impact of the vaccine delivered through the routine system plus catch up on disease transmission.

Outbreak response

CYD-TDV should not be considered as a tool for outbreak response. A dengue outbreak is a signal that an improved dengue control strategy is needed. When an outbreak occurs in an area that meets the criteria for routine introduction in relation to transmission intensity, vaccination with the 3-dose schedule as part of an overall dengue control strategy may be considered.

Special populations

Pregnant women: CYD-TDV is contraindicated in pregnant and lactating women because insufficient data have so far been gathered on its use in pregnancy. However, based on limited data generated from inadvertent pregnancies that occurred during clinical trials, there are no data to warrant termination of an inadvertent pregnancy should the vaccination have occurred anytime during pregnancy. If a woman becomes pregnant before all three doses have been administered, the remaining doses should be administered after lactation.

Immunocompromised: CYD-TDV is contraindicated in immunocompromised individuals. More data will be available from upcoming studies in HIV-infected individuals.

Travellers: CYD-TDV has not formally been licensed for use in travellers. In travellers who have already been previously infected with dengue, vaccination for travel to high transmission settings may be beneficial. Extrapolation of data from the Phase 3 trials suggests that in such persons there may be some protection after the first dose, but completion of the full 3-dose schedule is still recommended. In travellers unlikely to have already had dengue, vaccination may be substantially less beneficial (and there is a theoretical risk that it may be harmful), analogous to seronegative individuals living in endemic settings. Co-administration with other travel vaccines is not recommended.

Health care workers: There are no specific recommendations for health care workers.

Surveillance

Dengue surveillance should be strengthened, particularly in the context of emerging infections with clinical similarities to dengue. In areas of the world for which there is a paucity of data, further characterization of the burden of dengue, which appears to be growing, is needed. Harmonized case-definitions are encouraged to enhance data sharing and comparisons across regions.

Using surveillance data to monitor population impact of a vaccination program may be challenging as the year-to-year variability in dengue transmission may be greater than the expected vaccine impact. Long-term monitoring for severe dengue in vaccinated subjects to assess long-term effects of vaccination should be done in selected areas.

Other aspects

Due to the partial efficacy of the vaccine against dengue of any severity, careful communication is needed to inform vaccinees that they may still be at risk of dengue and of the importance of receiving all three doses and of adhering to other disease preventive measures.

An assessment of vaccine effectiveness, and the durability of that effectiveness, is a priority. Current data suggest substantially lower benefit of vaccination in seronegative individuals 9-45 years of age. There is a theoretical possibility that vaccination could do harm in this population. Although theoretical risks not supported by data should not impede rollout of this vaccine, it is critical to evaluate as soon as possible whether there is any risk to this population.

Research recommendations may be found in Section 11.7.

2. BACKGROUND

2.1Epidemiology

Dengue is a major public health problem with every WHO Region affected by dengue. Dengue viruses (DENVs) are members of the genus Flavivirus, within the family Flaviviridae. There are four serotypes (termed DENV-1 to DENV-4). All four serotypes circulate globally, with most endemic countries reporting circulation of all four serotypes in recent years [1].

Dengue is the most extensively spread mosquito-borne virus. In the last 60 years the incidence of clinical cases of dengue reported to WHO has increased 30-fold, with a much increased geographic range, including the expansion from predominantly urban to rural settings. Approximately 3.5 billion people live in dengue endemic countries; dengue is endemic in Asia and Latin America, and large parts of Africa, although data for Africa are sparse. The number of cases reported annually to WHO ranged from 0.4 to 1.3 million in the decade 1996–2005, and in 2010 was 2.2 million [2]. There is substantial under-reporting of dengue within health systems, and also underreporting to WHO [3]. A recent prediction based on available incidence and prevalence data and modelled globally estimated 390 million dengue infections per year in 2010 (95% credible interval 284–528 million), of which about 25%, 96 million (67–136 million), manifest clinically (with any severity of disease) [4]. The greatest number of infections was estimated to have occurred in Asia (204 million), followed by Africa (48 million), and the Americas (40 million)(Figure 1). WHO has estimated 500,000 hospitalizations for dengue annually, of which about 12,000 are fatal [5]. The case-fatality rate (CFR) is now low (<1%) due to advances in case management, although it varies according to location and how well severe dengue is managed medically. The number of people who are affected by dengue leads to tremendous burden on health care infrastructure as well as financial costs to the health sector, particularly during outbreaks when hospitals may become full or over capacity, and, in some cases, catastrophic household expenditures.

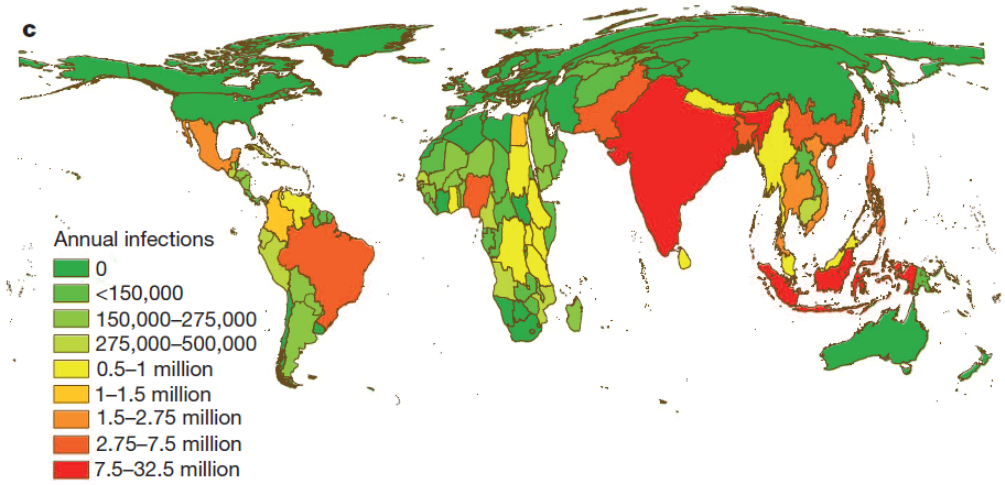


Figure 1 Cartogram of the annual number of infections in 2010 for all ages as a proportion of national or subnational geographical area [4].

Dengue viruses are primarily maintained in a human-to-mosquito-to-human cycle. The primary vector is the *Aedes aegypti* mosquito, which is highly domesticated. *Aedes albopictus* can also sustain DENV transmission. The spread of vectors following urbanization and the decline in vector-control efforts has partially contributed to the increased incidence of DENV infection. Additionally, factors such as population growth, globalization and travel, and climate change facilitate increased transmission of dengue.

Mosquito populations and their ability to transmit dengue appear to be highly dependent on climatic factors such as temperature and rainfall. Based on a review of nearly two decades of dengue surveillance data, a recent study found fluctuations in dengue transmission in 8 countries in South-East Asia closely following temperature patterns, with high incidence in 1997-1998 coinciding with elevated temperatures throughout the region and the strongest El Niño episode of the century [6].

Although reports of what were likely dengue outbreaks occurred as early as the mid-17th century, dengue could first be diagnosed definitively in the mid-1940s when the virus was able to be isolated [7]. Efforts shortly thereafter to eradicate the *Ae. aegypti* vector in the Americas to control Yellow Fever were successful in many countries, leading to reduced circulation of dengue and other mosquito-borne viruses. However, eradication across the continent fell short. As a result of a loss of political priority, DDT resistance, and other factors, mosquito control programs deteriorated and *Aedes* re-emerged in a broader geographic area. A number of dengue outbreaks were reported in the 1970s and 1980s, and despite renewed attempts to control the vector in the PAHO region, cases have continued to rise.

Transmission intensity as well as population structure and demographics can affect the age distribution of dengue infections and cases. Although there are many metrics used to measure transmission intensity, seroprevalence surveys are important for understanding age-specific infection rates, as many infections are clinically inapparent. Endemic settings are highly variable with respect to average age of infection. Figure 2 shows age-specific seroprevalence data from three settings, from low endemicity in Singapore (~10% seroprevalence by age 9 years) to high endemicity in Papua New Guinea (>90% seroprevalence at age 9 years).

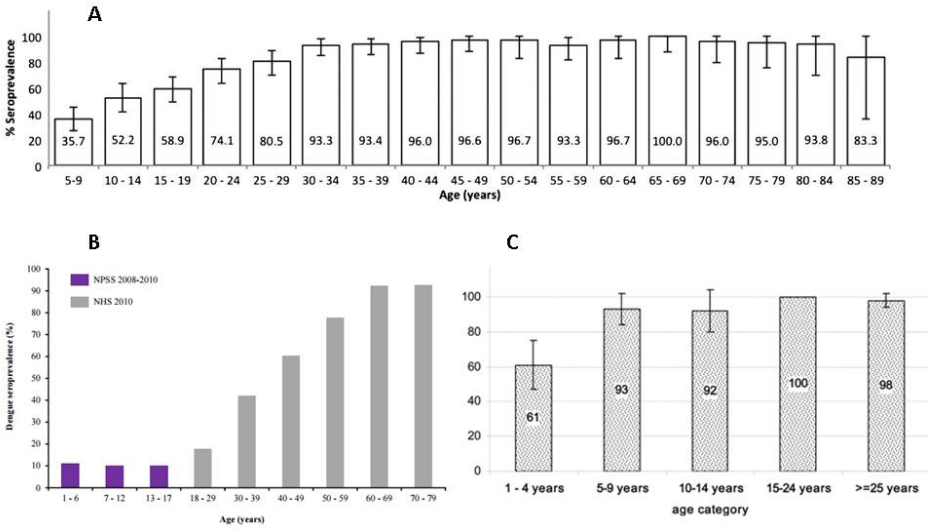


Figure 2 Examples of seroprevalence by age from localities in A) Mexico [8], B) Singapore [9], and C) Papua New Guinea [10].

Age distributions of infection are not static but change over time; in one province in Thailand, in 1980 96% of the population had been infected by dengue by age 11 years; in 2010, 65% of the population were infected by 11 years [11]. Similar variations in the ages at infection or of dengue disease have been seen in other settings [12], potentially due to demographic changes [13].

In addition to heterogeneity of transmission between countries and over time, heterogeneity at a local level makes country-wide generalizations difficult. Such heterogeneity could be based on geographic factors, such as elevation, or demographic factors, such as population density. While large differences may be seen in neighbouring municipalities (Figure 3), even further heterogeneity may be important at smaller spatial scales [14].

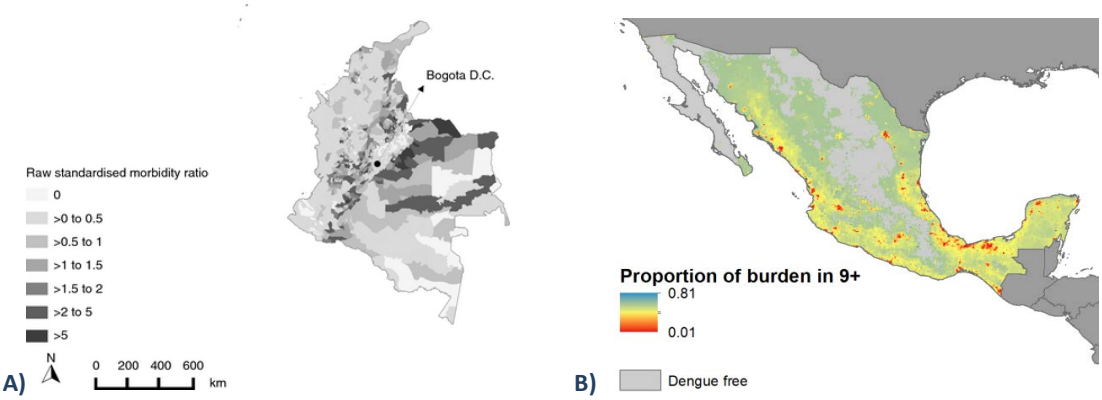


Figure 3 Heterogeneity in national patterns of dengue in A) Colombia, based on notified dengue cases by municipality[15], and B) Mexico, based on modelled proportion of dengue infections occurring in the 9 years of age and older population at fine spatial scale (Courtesy of O. Brady, Oxford University).

2.2 Disease and Diagnosis

The majority of DENV infections are either asymptomatic or mild. The incubation period is usually 4-7 days but can range from 3-14 days. The most common presentation is the sudden onset of fever accompanied by headache, pain behind the eyes, generalized myalgia and arthralgia, flushing of the face, anorexia, abdominal pain and nausea. Rash is frequently seen on the trunk, on the insides of the arms and thighs, and on plantar

and palmar surfaces and can be macular, maculopapular, morbilliform, scarlatiniform or petechial. Laboratory abnormalities may include leukopenia and thrombocytopenia. For the purpose of clinical management, WHO classifies dengue illness as (i) dengue with or without warning signs for progression towards severe dengue and (ii) severe dengue (Figure 4). Warning signs of severe dengue include abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy or restlessness, liver enlargement of >2 cm, or an increase in haematocrit concurrent with a rapid decrease in platelet count. Criteria for severe dengue include any sign of severe plasma leakage leading to shock or fluid accumulation with respiratory distress, severe bleeding, or severe organ impairment. A detailed clinical case classification of dengue is provided in the WHO Dengue Guidelines [16].

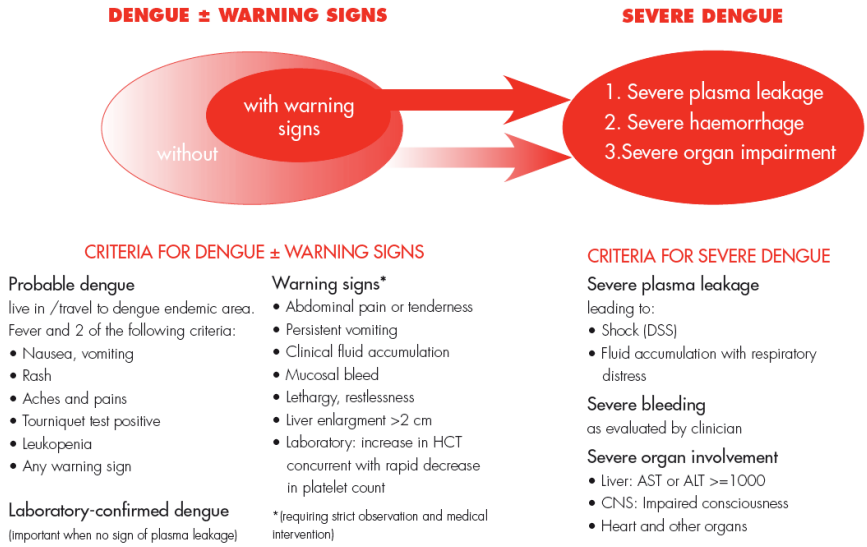


Figure 4 WHO dengue case classification and levels of severity [16].

There is no specific anti-viral treatment for dengue. Clinical management is based on supportive therapy, primarily judicious monitoring of intravascular volume replacement. Improvements in case management have reduced the case fatality rate of hospitalized dengue to less than 1%, whereas historically they were as high as 20% [17, 18].

Laboratory-confirmed dengue is diagnosed either by virus isolation, serology (MAC-ELISA, IgG ELISA, PRNT), or molecular methods (RT-PCR). Diagnosis by serology typically does not allow for serotyping the infecting virus (except by PRNT), and is also susceptible to cross-reactivity, variable sensitivity by timing of specimen collection, and the need for multiple samples (IgG acute and convalescent samples). PCR and detection of NS1 antigen offer more specific and early diagnosis (for PCR, 80-90% sensitivity and 95% specificity if applied in the appropriate time window).

2.3 Dengue pathogen and pathogenesis

Flaviviruses encompass a very dynamic and diverse group of species, and many are human pathogens. Flaviviruses are lipid-enveloped, positive-sense, single-stranded RNA viruses, approximately 55 nm in diameter. The virion RNA encodes a single open reading frame that is flanked by a 5' untranslated region (UTR) and a 3' UTR. Three structural proteins are derived by cleavages of the amino-terminal one third of the polyprotein: the capsid or core protein forms a "nucleocapsid" complex with virion RNA that lies within the lipid envelope. The premembrane (prM) and envelope (E) proteins are embedded in the lipid envelope via carboxy-terminal transmembrane domains and are displayed on the surface of virions. Cleavage of the carboxy-terminal two thirds of the polyprotein yields seven non-structural (NS) proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5.

NS1 plays various roles in the virus replication cycle while NS2A, NS2B, NS4A and NS4B are all small hydrophobic proteins with the central region of NS2B required for the functioning of the NS3 protease. The four DENV serotypes only share about 60-75% identity at the amino acid level, making them diverse viruses [19].

Following infection, resulting from the bite of an infected mosquito, the virus replicates in local dendritic cells. Subsequent infection of macrophages and activation of lymphocytes is followed by entry into the bloodstream. DENV primarily infect cells of the myeloid lineage, including macrophages, monocytes, and dendritic cells. There is also evidence of infection of hepatocytes and endothelial cells, although there is disagreement on the latter. Haematogenous spread is the likely mechanism for seeding of peripheral organs and the occasional reports of central nervous system infections.

2.4 Immune response to dengue infection and natural history of disease

Immune responses to dengue virus are only partially understood and complicated by the inter-relatedness of host responses to the four distinct serotypes. Dengue infection induces high-titered neutralizing antibody. Following a primary infection with one DENV, protection against the infecting serotype (homotypic protection) is believed to be life-long. Temporary cross-protection is induced to the other serotypes (heterotypic protection), lasting an average of around 2 years [20, 21]. Following waning of cross-neutralizing antibodies, the host-immune response may increase the severity of subsequent DENV infections with different serotypes. It is well accepted that severe disease is more likely to occur after a second dengue infection than after the first dengue infection with a relative risk of approximately 7 [14], although other studies have found higher [22, 23] or lower [24] relative risks. Following recovery from a second infection, broadly neutralizing antibody is induced (multitypic protection), such that severe disease with tertiary and quaternary infections is considered rare. The mechanism for more severe disease associated with a second infection is not well understood although antibody-dependent enhancement, cytokine storm, or cross-reactive T cells are hypothesized.

2.5 Dengue control measures

At present, the only method to control or prevent the transmission of dengue virus is through interventions directed at the vector. While no specific method is recommended, WHO recommends integrated vector management (IVM), which is defined as “a rational decision-making process for the optimal use of resources for vector control” [16]. A variety of approaches have been used in dengue control programs. There are many studies showing reductions in entomological indicators following vector control; however, there is a paucity of data to show an effect of vector control interventions on the incidence of human dengue cases [25]. Recent evidence from cluster-randomized trials in Nicaragua and Mexico suggest that community-based prevention efforts could have an effect on reducing dengue infection in children (as measured by paired saliva samples for IgG seroconversion) [26]. Few controlled studies have been conducted; thus many vector control interventions are undertaken without a strong evidence base for effectiveness. Some common interventions include:

- preventing mosquitoes from accessing egg-laying habitats by environmental management and modification, such as disposing of solid waste properly and removing artificial man-made mosquito habitats;
- covering, emptying and cleaning of domestic water storage containers on a weekly basis;
- applying appropriate insecticides or predators to outdoor water storage containers;
- using personal and household protection such as window screens, long-sleeved clothes, insecticide or repellent treated materials, coils and vaporizers;
- improving community participation and mobilization for sustained vector control;
- applying insecticides using space sprays during outbreaks as one of the emergency vector-control measures;

Vector control is best utilized as a routine preventive measure rather than as outbreak response. However, even for routine dengue control, the general consensus in the field of vector control for dengue is that current tools are difficult to standardize and evaluate, and their application requires a trained workforce, as well as inter-sectoral and community participation. Though countries such as Singapore and Cuba have been able to implement very high levels of vector control and have to some extent moderated endemicity and outbreaks, problems are faced with widespread implementation, sustainability and cost. Many current tools require a robust evaluation against clinical endpoints (rather than entomological endpoints) to assess their impact on disease. For new vector control tools, such as RIDL (Release of Insects with Dominant Lethality (sterile males)) and Wolbachia (a bacteria found in many insects that reduces mosquitoes ability to transmit dengue by multiple mechanisms), there are plans in place to evaluate the effectiveness against dengue. There are also ongoing efforts to conduct such evaluations for traditional vector control tools.

However, given their importance to dengue control programs, and the fact that these vectors carry other viruses (e.g. Zika and Chikungunya), the use of any new tools, such as vaccination, would be in the context of existing vector control measures. Better data on the effectiveness of vector control against dengue are needed to be able to redesign dengue control programs to optimize the package of interventions, also in consideration of disease transmission of different *Aedes* circulated pathogens.

3. DENGUE VACCINES

3.1 Clinical pipeline

There have been efforts to develop dengue vaccines for decades, but it has proven to be one of the more difficult pathogens against which to develop a vaccine for a variety of reasons. Importantly, it has been difficult to develop a vaccine that induced balanced protection without immunologic interference following simultaneous vaccination against all four dengue serotypes; this is not necessarily a prerequisite but has been considered highly desirable given the immune pathology resulting from sequential natural infections. There is no good animal model for dengue; non-human primates develop some viraemia but no clinical disease. There is no established correlate of protection, and the assay used to measure neutralizing antibodies (PRNT) is limited in its relevance to thresholds of protection. Both quantitative and qualitative aspects of the immune response are likely to be important; a single measurement may be insufficient, protective levels may vary by serotype, and/or be vaccine-specific. Because there is no specific antiviral treatment for dengue, the use of human infection models to evaluate vaccine candidates have been controversial, although there are attenuated challenge strains approved under US FDA Investigational New Drug (IND) that will soon be used for vaccine candidate profiling. Theoretical concerns about immune enhancement following waning immunity have necessitated relatively long follow up of clinical trial participants [27].

In the dengue vaccine clinical pipeline there is one vaccine registered (developed by Sanofi Pasteur and the focus of this background paper) and at least five candidates in clinical development but not yet licensed. The two most advanced candidates under clinical development are live attenuated (recombinant) vaccines developed by the U.S National Institutes of Health (NIH) and licensed to several manufacturers, and by Takeda.

TV003 and TV005 (which are identical vaccine candidates except for the dosing level of the DEN2 component) were developed by the US NIH and are based on wild-type strains with targeted mutations to attenuate the virus [28]. Vaccine virus serotypes 1, 3, and 4 are based on complete viruses, while serotype 2 is a recombinant virus based on the serotype 4 vaccine strain with the structural proteins replaced by those of serotype 2. TV003 or TV005 has been licensed to several manufacturers, including Butantan, VaBiotech, Panacea, Serum Institute of India and Merck. Phase 2 studies are underway in Brazil and Thailand. Butantan has started a Phase 3 trial.

Takeda is also developing a live recombinant vaccine, TDV (formerly DENVax). This tetravalent candidate includes a whole attenuated DEN2 virus and recombinant DEN1, DEN3, and DEN4 using the DEN2 backbone. There have been a number of ongoing and completed Phase 1 and Phase 2 trials in both endemic and non-endemic settings, evaluating different dosing schedules and a variety of formulations and routes of administration (including traditional needle-syringe mechanism, a needle-less injector, and a needle-free Pharmaject Injector). A multicenter Phase 3 study is being planned.

Other candidates and approaches have been evaluated, or are currently under evaluation, in Phase 1 trials, include a tetravalent purified inactivated vaccine (GSK/Walter Reed Army Institute of Research), a tetravalent recombinant subunit vaccine based on the dengue wild-type pre-membrane and truncated envelope protein (Merck), a monovalent plasmid DNA vaccine (US Navy Medical Research Center), and an inactivated vaccine/live attenuated vaccine heterologous prime boost (Walter Reed Army Institute of Research).

3.2 Technical Specifications of CYD-TDV (Dengvaxia®)

CYD-TDV (Dengvaxia®) is a prophylactic, tetravalent, live attenuated viral vaccine developed by Sanofi Pasteur. The indication from the first licenses (Mexico, Philippines, Brazil, El Salvador, and Paraguay) is for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3, and 4 in individuals 9 through 45 or 60 years of age (depending on the license), living in dengue endemic areas. The vaccination schedule consists of 3 injections of 0.5 mL administered at 6-month intervals by the sub-cutaneous route. A time window of +/- 20 days was specified as acceptable for doses 2 and 3.

The active substances contained in the CYD dengue vaccine are 4 live attenuated viral recombinants representing serotypes 1, 2, 3, and 4. Each monovalent CYD recombinant is obtained separately by replacing the genes encoding the pre-membrane (prM) and envelope (E) proteins of the structural proteins in the attenuated yellow fever (YF) 17D virus genome with the corresponding genes of the 4 wild type dengue serotypes 1, 2, 3 and 4. The final formulation contains 4.5-6.0 log10 median cell-culture infectious doses ($CCID_{50}$) of each live, attenuated, dengue serotype 1, 2, 3 and 4 viruses.

CYD-TDV is presented in a single-dose vial or in a 5-dose multi-dose vial. It is a sterile, freeze-dried product to be reconstituted before injection with either a sterile solution of 0.4% sodium chloride for the single-dose presentation or a sterile solution of 0.9% sodium chloride for the 5-dose presentation. After reconstitution, one dose (0.5 mL) is to be administered by the subcutaneous (SC) route. The diluent is provided as a pre-filled syringe for single-dose presentation, or in a vial for the multi-dose presentation.

The CYD-TDV dengue vaccine contains no adjuvant or preservatives. No material of biological origin (animal or human) is used in the manufacturing process of the CYD dengue virus seed lot system, Vero cell banking system and CYD Drug Substance (DS) and Drug Product (DP). Extraneous agent tests (in vivo tests on animals, in vitro tests on several cell substrates, molecular biology) were carried out along the manufacturing process of the seed lots, cell banks and DS and none showed the presence of adventitious agents.

Based on the package inserts vaccination is contraindicated in: 1) individuals with a history of severe allergic reaction to any component of the dengue vaccine or after prior administration of the dengue vaccine or a vaccine containing the same components; 2) individuals with congenital or acquired immune deficiency that impairs cell-mediated immunity; 3) individuals with symptomatic Human Immunodeficiency Virus (HIV) infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function; and 4) pregnant or breastfeeding women. Administration should be postponed in individuals suffering from moderate to severe febrile or acute disease.

3.3 Development of CYD-TDV

CYD-TDV has been under development for the last two decades. The platform used for CYD-TDV is the same as that used for the Japanese encephalitis vaccine, IMOJEV®, which was first licensed by Australia in 2010. A number of non-clinical assessments were undertaken with YF17D recombinant flavivirus vaccines against dengue viruses, West Nile Virus, and Japanese encephalitis virus to evaluate theoretical environmental risks related to vaccine virus transmission through mosquitoes, reversion to virulence, and recombination [29].

These recombinant vaccines induce no or low viraemia in human recipients, which is considered below the threshold for transmission to mosquitoes. No oral infection of mosquitoes was induced, and no transmission was observed when infected directly. Despite being a RNA virus, the YF17D vaccine genome was found to be very stable. Natural recombination (intragenetic or intergenetic) is considered unlikely, and artificial recombinants produced in the laboratory were still attenuated. Full genome sequences of the four recombinant dengue vaccine viruses were established for premaster seed lots, master seed lots, bulk, and bulk+10 passages. High genomic stability was seen, with only 9 mutations across all four vaccine strains. All except one were in the non-structural region. The 8 non-silent mutations occurred early in the process and were conserved moving forward.

A number of Phase 1 and 2 studies have been conducted around the world, and, including the Phase 3 studies, more than 25,000 individuals have received at least 1 dose of vaccine (Table 1). The development program was consistent with that recommended by WHO [27].

Following Phase 1 and 2 studies to select formulation, dose, and schedule, a proof-of-concept Phase 2b efficacy study was conducted in Thailand (CYD23/57), which provided initial estimates of efficacy. The primary objective of the phase 2b study was to assess the efficacy of CYD-TDV in preventing dengue disease, after completion of the vaccination schedule of three doses given 6 months apart. Additional objectives included the evaluation of vaccine safety and immunogenicity. The study population consisted of 4,002 children aged 4 to 11 years in Ratchaburi Province, Thailand. The definition of fever, precipitating a diagnostic test for dengue, was slightly different to that used in the Phase 3 trials. The trial included 2 years of active follow up, and then 4 years of hospital-based follow up. Due to the wealth of data from the Phase 3 trials, which are larger and across varied settings, and thus allow for greater interrogation of the data, results from the Phase 3 trials are emphasized.

Table 1 Clinical database; Number of persons who received at least one vaccine dose, by age and endemicity. Provided by manufacturer on request.

	<9 years*	9-16 years	17-45 years	46-60 years**
Non-endemic settings	Safety: Not Done (N.D.) Immunogenicity: N.D. Efficacy: N.D.	Safety: N.D. Immunogenicity: N.D. Efficacy: N.D.	Safety: 638 Immunogenicity: 632 Efficacy: N.D.	Safety: 241 Immunogenicity: 241 Efficacy: N.D.
Endemic settings	Safety: 5,689 Immunogenicity: 1,296 Efficacy: 5,166	Safety: 19,120 Immunogenicity: 2,810 Efficacy: 18,262	Safety: 668 Immunogenicity: 294 Efficacy: N.D.	Safety: N.D. Immunogenicity: N.D. Efficacy: N.D.

<9 years*: Outside of claimed age indication

46-60 years**: Outside of the licensed indication in some countries

3.4 Overview of Phase 3 Trials on CYD-TDV

CYD-TDV has been evaluated in two parallel Phase 3 clinical trials, known as CYD14 and CYD15. CYD14 was conducted in 5 countries in Asia (Indonesia, Malaysia, Philippines, Thailand, and Vietnam), with 10,275 participants aged 2-14 years at first vaccination. CYD15 was conducted in 5 countries in Latin America (Brazil, Colombia, Honduras, Mexico, and Puerto Rico (US)), with 20,869 participants aged 9-16 years at first vaccination. In each of these trials, participants were randomized to vaccine and placebo in a 2:1 ratio.

Because the physical appearance of the vaccine and placebo was different, unmasked trial staff was responsible only for preparation and administration of injections and were not involved in the follow-up of trial participants. For the ascertainment of trial endpoints the trials were observer-masked. All serology testing was also performed in a blinded manner. The dosing schedule and trial design were identical in the two Phase 3 studies, and each was designed to have similar statistical power to assess vaccine efficacy, based on the expected disease incidence in the study locations. Together, these trials included over 30,000 participants aged 2 to 16 years.

Table 2 Overview of Phase 3 Trials design and status

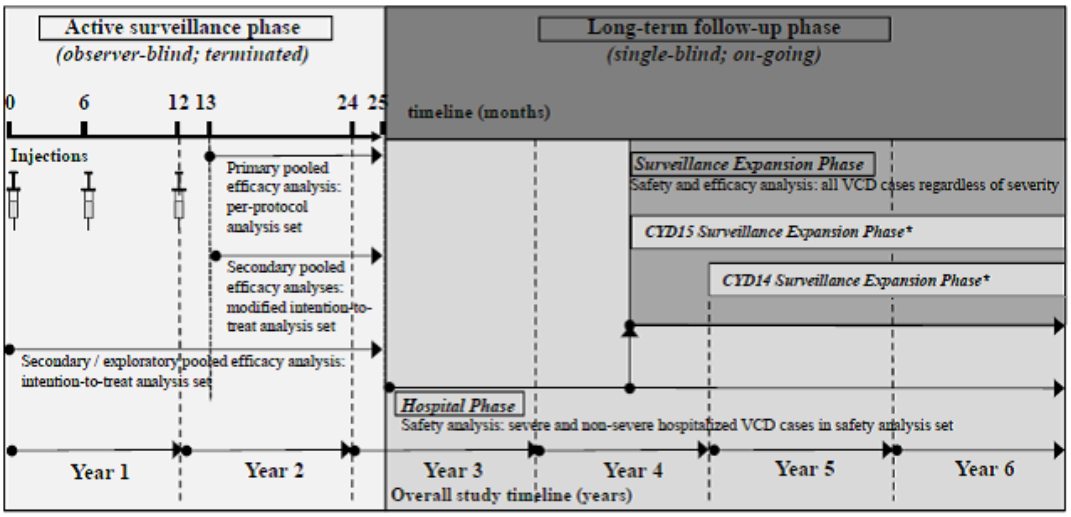
	CYD14	CYD15
Trial size	10,275	20,869
Randomization CYD:Placebo	2:1	2:1
Ages included	2-14 years	9-16 years
Countries participating	Indonesia, Malaysia, Philippines, Thailand, and Vietnam	Brazil, Colombia, Honduras, Mexico, and Puerto Rico (US)
Primary endpoint (per protocol)	Vaccine efficacy after 3 vaccinations at 0, 6, and 12 months (VE measured from 28 days after the 3rd dose) in preventing symptomatic virologically-confirmed dengue cases, regardless of the severity, due to any of the four serotypes up to 13 months pose-dose 3.	Vaccine efficacy after 3 vaccinations at 0, 6, and 12 months (VE measured from 28 days after the 3rd dose) in preventing symptomatic virologically-confirmed dengue cases, regardless of the severity, due to any of the four serotypes up to 13 months pose-dose 3.
Study start date	June 2011	June 2011
End of Active Phase for primary endpoint	December 2013	April 2014
Estimated completion date	November 2017	April 2018

The study protocols included an active phase of follow-up for 13 months after the last dose of vaccine in the series (i.e. 25 months from dose 1) for the primary efficacy endpoint and included a hospital-based follow-up period of four additional years for safety evaluation, which is ongoing.

During the Active Phase of surveillance (Years 1-2), participants attended five visits at months 0, 6, 12 (for vaccination) and months 13 and 25 for follow-up. During the 2-year period children were monitored for febrile illnesses through weekly contact with participants or their parent/guardian, and in CYD14 by school absenteeism as well. For participants with an acute febrile illness, blood samples were taken for diagnosis. Virologically-confirmed dengue was defined as acute febrile episode (temperature ≥38°C on ≥2 consecutive days) and a positive NS1 or rtPCR test.

During the Hospital Phase (Years 3+) participants who were admitted to hospital with a febrile illness (temperature ≥38°C on ≥2 consecutive days) were tested for dengue infection (as described above) but children with febrile illnesses who were not admitted to hospital were not monitored. Thus, relative risks against hospitalized and severe dengue could be estimated (but not the milder forms identified through active surveillance in Years 1-2). Study investigators, parent/guardians, and participants will all remain masked to vaccination status until the hospital phase of the trial is complete.

A Surveillance Expansion Phase (SEP) was initiated in Years 4 and 5 of the Phase 3 trials. The SEP, for which re-consenting of participants is currently ongoing, will transition to an active surveillance follow up among participants who consent (those unwilling are still followed in the Hospital Phase follow up).



VCD: virologically-confirmed dengue; Per-protocol analysis set VCD from D28 post injection 3 to M25; Modified intention-to-treat analysis set: VCD from D28 after all 3 injections, regardless of protocol deviations; Intention-to-treat analysis set: VCD from D0 to M25 after ≥1 injection; Safety analysis set: participants who received ≥1 dose: participants analyzed according to the first dose treatment received
*As of February 2016, re-consenting process for the Surveillance Expansion Phase is still ongoing

Figure 5 Summary of Phase 3 trial design. Provided by manufacturer on request.

Severe dengue was classified based on clinical characteristics in two ways: 1) met criteria for the 1997 WHO classification for dengue haemorrhagic fever (DHF), or 2) met criteria set forth by the Independent Data Monitoring Committee (IDMC)[4]. For the purposes of the SAGE review, Working Group emphasis has been placed on severe disease as assessed by the IDMC due to its consideration of broader organ impairment.

Blood samples were taken from all trial participants at month 13 (one month post-dose 3). Pre-vaccination and month 7 blood samples were taken in a subset of participants in each trial, the analysis set for immunogenicity (immunogenicity subset) to test concentrations of dengue neutralizing antibody measured by the Vero cell based plaque reduction neutralisation test ($PRNT_{50}$). In CYD14 (immunogenicity subset N=1983) and CYD15 (immunogenicity subset N=1944), participants who were enrolled the early part of the trials in each country were included in the immunogenicity and reactogenicity subsets.

Serostatus at baseline was assessed for those in the immunogenicity subset. While $PRNT_{50}$ is non-diagnostic, participants with $PRNT_{50} \geq 10$ against one or more serotypes were considered seropositive at baseline, which was interpreted as having been exposed to at least one dengue virus prior to vaccination. All other participants

[4] IDMC classified dengue cases as severe using the following criteria: Virologically-confirmed dengue fever, i.e. temperature ⩾38°C on ⩾2 consecutive days and virological confirmation, and at least one of the following:

- Platelet count ⩽$100x10^9$/L and bleeding (tourniquet, petechiae or any bleeding) and plasma leakage (effusion on chest x-ray or clinically apparent ascites including imaging procedures or hematocrit >20% above baseline recovery level or standard for age if only one reading).
- Shock (pulse pressure ⩽ 20 mmHg in a child or adolescent, or hypotension [⩽ 90mmHg] with tachycardia, weak pulse and poor perfusion).
- Bleeding requiring blood transfusion
- Encephalopathy i.e., unconsciousness or poor conscious state (Glasgow Coma Scale (GCS) score) or convulsions not attributable to simple febrile convulsion or focal neurological signs.
- Liver impairment (AST >1000 U/L or prothrombin time, international normalized ratio >1.5)
- Impaired kidney function (serum creatinine ⩾1.5 mg/dL)
- Myocarditis, pericarditis or heart failure (clinical heart failure) supported by chest X ray, echocardiography, electrocardiogram or cardiac enzymes where they were available

were considered seronegative, which was interpreted as dengue non-immune. Age-specific seropositivity proportions are presented in Table 3.

Table 3 Proportion of CYD14 and CYD15 participants testing positive for neutralizing antibodies to one or more dengue serotype by $PRNT_{50}$ [30, 31]

Age group	CYD 14	CYD15
2-5 years	51%	NA
6-11 years	72%	75%**
12-16 years	81%*	84%
Total Trial Population	68%	79%

* 12-14 years ** 9-11 years

4. CYD-TDV VACCINE EFFICACY IN THE ACTIVE FOLLOW-UP

4.1 Vaccine efficacy against VCD from Phase 3 trials during the period of active follow-up

Vaccine efficacy against virologically-confirmed dengue (VCD) of any severity was designed to be evaluated only during Years 1 and 2 of the efficacy trials, when active surveillance was in place. The per protocol analysis of vaccine efficacy was based on follow up time from Month 13 to Month 25 (1 month post-dose 3, for 12 months). The per protocol vaccine efficacy is shown in Table 4.

Table 4 Vaccine efficacy during the active phase of surveillance, by serotype (pre-specified analyses, per protocol population, duration of follow up: study months 13-25) [30-32].

Outcome	CYD14	CYD15	Pooled
VCD-DENV1-4	56.5% (43.8-66.4)	60.8% (52.0-68.0)	59.2% (52.3-65.0)
VCD-DENV1	50.0% (24.6-66.8)	50.3% (29.1-65.2)	50.2% (35.6-61.5)
VCD-DENV2	35.0% (-9.2, 61.0)	42.3% (14.0-61.1)	39.6% (18.7-55.2)
VCD-DENV3	78.4% (52.9-90.8)	74.0% (61.9-82.4)	74.9% (65.1-82.0)
VCD-DENV4	75.3% (54.5-87.0)	77.7% (60.2-88.0)	76.6% (65.0-84.4)

Vaccine efficacy against dengue of any serotype was 56.5% (95%CI 43.8-66.4) in CYD14, and 60.8% (95%CI 52.0-68.0) in CYD15. In both trials, vaccine efficacy was lower against serotypes 1 and 2 than against serotypes 3 and 4. Vaccine efficacy estimates were similar across the two Phase 3 trials despite variable epidemiological settings and ages at vaccination (2-14 years in CYD14 and 9-16 years in CYD15).

Aside from the vaccine efficacy estimates reported above, the manufacturer calculated all other secondary outcome vaccine efficacy parameters using the intention-to-treat (ITT) population for efficacy (follow up starting with administration of dose 1, Month 0-Month 25). These are displayed in Table 5.

Table 5 Vaccine efficacy (intention to treat population) against VCD of any severity during the active phase of surveillance, by serotype, serostatus, (pre-specified analyses), duration of follow up: study months 0-25) [30-32]. VE estimates in those >9 years pooled are post-hoc analysis for CYD14, pre-specified analyses CYD15.

Outcome	Study Population	CYD14	CYD15	Pooled	Pooled ≥ 9 years
VCD-DENV1-4	All	54.8% (46.8-61.7)	64.7% (58.7-69.8)	60.3% (55.7-64.5)	65.6% (60.7-69.9)
	2-5 years	33.7% (11.7-50.0)	NA	NA	NA
	6-11 years	59.5% (48.9-68.0)	61.7% (52.3-69.3)**	Not published	Not published
	12-16 years	74.4% (59.2-84.3)*	67.6% (59.3-74.3)	Not published	Not published
	Seropositive	74.3% (53.2-86.3)	83.7% (62.2-93.7)	78.2% (65.4-86.3)	81.9% (67.2-90.0)
	Seronegative	35.5% (27,0; 66,6)	43.2% (-61,6; 80,0)	38.1% (-3.4-62.9)	52.5% (5.9-76.1)
VCD-DENV1	Full	54.5% (40.9-64.9)	54.8% (40.2-65.9)	54.7% (45.4-62.3)	58.4% (47.7-66.9)
VCD-DENV2	Full	34.7% (10.4-52.3)	50.2% (31.8-63.6)	43.0% (29,3; 53,9)	47.1% (31.3-59.2)
VCD-DENV3	Full	65.2% (43.3-78.9)	74.2% (63.9-81.7)	71.6% (63.0-78.3)	73.6% (64.4-80.4)
VCD-DENV4	Full	72.4% (58.5-81.7)	80.9% (70.9-87.7)	76.9% (69.5-82.6)	83.2% (76.2-88.2)

*12-14 years , **9-11 years

Vaccine efficacy estimates against VCD for all serotypes were similar in the per protocol analysis (56.5% and 60.8% for CYD14 and CYD15) and in the ITT analyses (54.8% and 64.7% for CYD14 and CYD15, respectively). The overall pooled estimate for CYD14 and CYD15 combined for VCD of any serotype in the 2 years post-dose 1 was 60.3% (95%CI 55.7-64.5). Vaccine efficacy was lower in the youngest age group of 2-5 years (CYD14 only) at 33.7%, and it was highest in the oldest age groups (VE 74.4% in CYD14 and 67.6% in CYD15 among participants 12-14 or 12-16 years of age, respectively). Vaccine efficacy was higher in individuals who were seropositive at baseline (pooled VE against dengue of any serotype was 78.2%) compared to those who were seronegative at baseline (pooled VE against dengue of any serotype was 38.1%, the confidence interval for which included 0%). The limited number of individuals in the immunogenicity subset, for which serostatus at baseline was known, makes it difficult to interpret analyses further stratifying this group (e.g. by age).

The summary vaccine efficacy estimates reported above have included children of all ages in the Phase 3 trials, including those <9 years who are not included in the currently indicated age ranges for licensing. An analysis was done limited to those ≥9 years of age in CYD14 (post-hoc) and CYD15 (full trial population in CYD15, pre-specified). Pooled efficacy estimates in the 2 years following dose 1 are similar to those for the full trial population. Vaccine efficacy was 65.6% (95%CI 60.7-69.9) against VCD of any serotype in the ≥9 years population, and in the subset for whom baseline serostatus was assessed the efficacy of 81.9% (95%CI 67.2-90.0) in those seropositive at baseline and 52.5% (95%CI 5.9-76.1) in those seronegative at baseline. Vaccine efficacies among those seropositive and seronegative at baseline who were <9 years were 70.1% (95%CI 32.3-87.3) and 14.4% (95%CI -111-76.1), respectively [32].

When age is modelled as a continuous variable, VE against VCD is relatively stable in the indicated age range (9-16 years) from Month 0 to Month 25 (no data on VCD beyond Month 25 due to change in from active to hospital-based surveillance in the trial) (Figure 6).

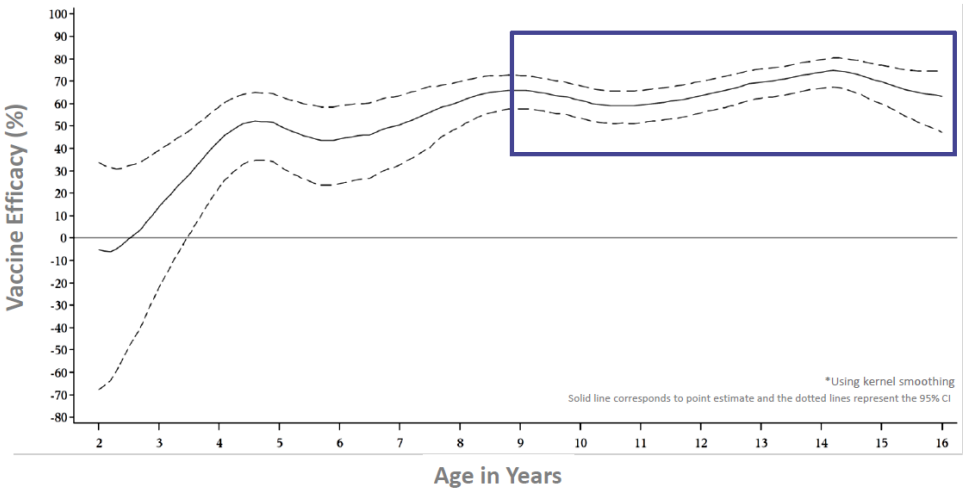


Figure 6 VE against symptomatic virologically-confirmed dengue cases during the whole Active Phase due to any of the 4 serotypes according to age, using kernel smoothing - CYD14 & CYD15 (2-16 years) [33].

Vaccine efficacy estimates varied by infecting serotype, serostatus at baseline, and age (although age and serostatus are highly correlated). Serotype distribution and transmission intensity varied across trial sites. Thus, vaccine efficacy estimates in the trials at the country level vary at least in part due variations in these characteristics between countries (Table 6). For example, vaccine efficacy was high in Brazil (77.5% against VCD of any serotype), where about 75% of the population was seropositive at baseline and there was a DENV4 outbreak, against which serotype the vaccine efficacy was high. Vaccine efficacy was lowest in Mexico, where only about 50% were seropositive at baseline, and there was a high burden of DENV1 and DENV2, against which serotypes the VE was lower. However, such correlations were not as clear in CYD14.

Table 6 Seropositivity and distribution of dengue serotypes in among trial participants by country and vaccine efficacy (ITT population of all ages included in trial, follow up from study month 0-25) [30, 31] and provided by manufacturer on request.

Study	Country	N (% of total in trial)	Baseline dengue seropositivity	DENV-1 cases in placebo	DENV-2 cases in placebo	DENV-3 cases in placebo	DENV-4 cases in placebo	VE
CYD14 (2-14 years)	Indonesia	1870 (18%)	80.9%	11	19	8	4	54.3% (28.0-71.0)
	Malaysia	1401 (14%)	47.0%	5	5	3	2	79.0% (52.3-91.5)
	Philippines	3501 (34%)	78.1%	87	22	17	33	53.9% (41.7-63.6)
	Thailand	1170 (11%)	67.7%	16	17	11	2	51.8% (25.3-68.9)
	Vietnam	2333 (23%)	54.2%	7	11	4	26	51.1% (26.1-67.6)
CYD15 (9-16 years)	Brazil	3548 (17%)	73.5%	9	0	0	72	77.5% (66.5-85.1)
	Colombia	9743 (47%)	92.2%	58	33	67	9	67.5% (58.3-74.7)
	Honduras	2799 (13%)	85.7%	6	20	39	0	71.1% (57.0-80.7)
	Mexico	3464 (17%)	53.1%	25	30	0	1	31.3% (1.3-51.9)
	Puerto Rico	1315 (6%)	56.2%	11	1	0	1	57.6% (-2.5-82.8)

In CYD23 (Phase 2b trial in Thailand), the vaccine efficacy estimate against VCD of any serotype in the ITT analysis was 34.9% (95% CI 6.7% to 54.3%) but was not statistically significant in the per protocol analysis, 30.2%

(95% CI -13.4% to 56.6%) [34]. Statistically significant efficacy estimates were reported for three of the four dengue virus serotypes (DENV1, DENV3, and DENV4) after at least one vaccine dose (ITT), but not after three doses (per protocol). These results are consistent with the lower vaccine efficacy generally seen against DENV2 (per protocol vaccine efficacy against DENV2 was 9.2%, 95%CI -75.0-51.3); around half of the cases of dengue in the placebo group in this trial were DENV2.

4.2 Vaccine efficacy against hospitalization for dengue and severe dengue during the period of active follow-up

Vaccine efficacy against VCD resulting in hospitalization, as well as against severe dengue, was higher in the 25 months following dose 1 than for VCD of any severity (Table 7). Across all ages, pooled VE against hospitalized dengue was 72.7% (95%CI 62.3-80.3), and 80.8% (95%CI 70.1-87.7) in participants first vaccinated ≥ 9 years of age. Vaccine efficacy against hospitalization for VCD was higher across all serotypes than VCD (Table 5 and Table 7). Notably, hospitalization rates in the placebo arm varied substantially across countries, ranging from 4.9% of VCD episodes in Brazil to 45.5% in Indonesia [35]. Vaccine efficacy against severe dengue was 79.1% (95%CI 60.0-89.0) in the first 25 months of follow up in the two trials combined, and it was 93.2% (95%CI 77.3-98.0) in participants ≥9 years of age.

The number of severe or hospitalized episodes was too small to undertake meaningful analyses stratifying by other factors.

Table 7 Vaccine efficacy against hospitalized or severe VCD during the active phase of surveillance (pre-specified analyses, intention to treat population, duration of follow up: study months 0-25)[32].

Outcome	CYD14	CYD15	Pooled	Pooled ≥ 9 years
Severe (IDMC) VCD	70.0% (35.7-86.6)	95.5% (68.8-99.9)	79.1% (60.0-89.0)	93.2% (77.3-98.0)
Hospitalized VCD	67.4% (50.6-78.7)	80.3% (64.7-89.5)	72.7% (62.3-80.3)	80.8% (70.1-87.7)
Hospitalized VCD-DENV1	71.5% (44.1-86.0)	73.2% (27.8-91.0)	72.1% (52.9-83.4)	Not published
Hospitalized VCD-DENV2	50.2% (-12.7-78.0)	80.1% (45.7-93.7)	65.7% (39.3-80.6)	Not published
Hospitalized VCD-DENV3	73.2% (27.6-90.9)	83.4% (33.6-97.1)	77.4% (52.2-89.3)	Not published
Hospitalized VCD-DENV4	77.9% (20.8-95.0)	91.7% (31.8-99.8)	83.5% (54.5-94.0)	Not published

4.3 Vaccine efficacy up to two years post randomisation, by dose

The indicated vaccine schedule is three doses administered 6 months apart. Completion of the 3-dose series in the Phase 3 trials was very high (over 90%), such that it is not possible to estimate efficacy after each dose, except in the 6 months following each dose. In the pooled analysis in the indicated age range (≥ 9 years*)*, VE between doses 1 and 2 was 70.8% (95%CI 58.1-79.6), 66.6% (95%CI 54.5-75.5) between doses 2 and 3, and 62.4% (95%CI 51.4-70.9) between dose 3 and 6 months post-dose 3 (data provided by manufacturer on request). The overall VE during the full active phase was 65.6% (95%CI 60.7-69.9). The rapid protective effect of 1 dose can be seen in the Kaplan-Meier curves, showing the accumulation of cases for vaccinated and control children. The curves start to diverge within a short period of the first dose (Figure 7).

The protective effect of doses 1 and 2 beyond 6 months after these doses, is unknown, nor is the additional protection derived from doses 2 and 3 known. Doses after the first may influence the duration of efficacy and may have different effects in those seropositive or seronegative at baseline. These remain research questions.

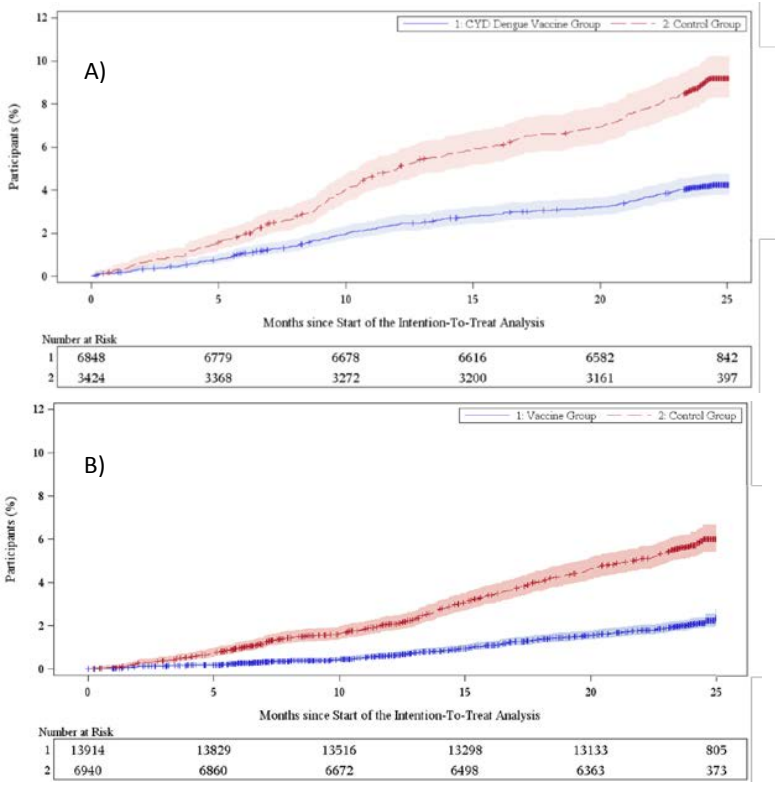


Figure 7 Cumulative incidence curve for virologically-confirmed dengue during the active phase due to any serotype - Full Analysis Set for Efficacy - CYD15(ITT population, follow up from study month 0-25), A) CYD 14 and B) CYD15. Modified from [30, 31]

5. DENGUE AND DURATION OF PROTECTION BEYOND 2 YEARS OF FOLLOW-UP

The data presented so far have covered the active follow-up phase of the trials, months 0-25. Following this period, the participant follow up switched to hospital-based (as planned in the trial protocol for years 3-6). Thus, in this period it was no longer possible to assess VE against VCD (though will be with the surveillance expansion phase currently initiated). The continuing follow up for hospitalized and severe dengue was undertaken as a safety endpoint. To make clear this distinction, vaccine effects are reported as relative risks (rather than as VEs).

The long term follow-up data presented in this section rely on analyses performed by the manufacturer as an ongoing safety management supporting the IDMC evaluation of the safety. It contains the first 2 complete years of hospital phase from CYD14 (Study Years 3 and 4, abstract submitted to 5th Pan American Dengue Research Network Meeting; Panama 20-14 April 2016: Long-Term Safety of a CYD-TDV Dengue Vaccine in Asia Dengue Endemic Countries), Year 3 from CYD15 and Years 3 and 4 from CYD57 [32]. In addition, data provided by manufacturer upon request are also presented for CYD14 (partial Year 5), CYD15 (partial Year 4 and Year 5), and CYD57 (Year 5 complete and partial Year 6). Finally, cumulative Relative Risks over the entire study are also provided (data provided by manufacturer upon request).

5.1 Effects on dengue hospitalizations more than 2 years after trial entry

During the course of the hospital-based surveillance, a signal emerged from the youngest age group (2-5 years, an age group only included in CYD14). During both Years 1 and 2 of active follow-up, the RR of hospitalized dengue in the 2-5 year age group was 0.6 (. During Year 3, there were 15 hospitalized cases in the CYD group compared to 1 hospitalized case in the placebo group (2:1 randomization), a RR of 7.45 (95%CI 1.15-313.80) (Table 8). During Year 4 and Year 5, the cumulative relative risk for Year 3 onwards diminished to 1.424 (95%CI 0.58-3.99) and 1.495 (95%CI 0.27-15.15), respectively. The cumulative relative risk during the entire trial period to date is 1.256 (95%CI 0.76-2.13). The 2-5 year age group was not included in CYD15.

Table 8 Vaccine effect on hospitalized dengue of any severity (ITT population) over time for CYD14, CYD15, and CYD23/57. [32] and provided by manufacturer on request.

		CYD14			CYD15			CYD23/57		
Age Group	Time Period	CYD cases	Control cases	RR (95%CI)	CYD cases	Control cases	RR (95%CI)	CYD cases	Control cases	RR (95%CI)
2-5 Years CYD 14 N=2451 CYD23/57 (starting at 4) N=623	Year 1 (Active)	8	6	0.644 (0.20-2.32)	Not included in trial population			1	2	0.239 (0.00-4.58)
	Year 2 (Active)	9	7	0.641 (0.21-2.02)				3	1	1.413 (0.11-74.17)
	Year 3 (Hospital)	15	1	7.45 (1.15-313.80)				5	1	2.443 (0.27-115.54)
	Year 4 (Hospital)	20	7	1.424 (0.58-3.99)				5	3	0.814 (0.16-5.24)
	Year 5 (Hospital/SEP)	6	2	1.495 (0.27-15.15)				4	0	+inf (0.32- +inf)
	Year 6 (Hospital)	NA	NA	NA				11	4	1.344 (0.40-5.76)
	Cumulative to date	**58**	**23**	**1.256 (0.76-2.13)**				**29**	**11**	**1.274 (0.62-2.83)**
6-8 Years CYD 14 N=2791 CYD23/57 N=1513	Year 1 (Active)	5	12	0.209 (0.06-0.64)	Not included in trial population			4	3	1.274 (0.62-2.83)
	Year 2 (Active)	8	9	0.446 (0.15-1.3)				18	13	0.670 (0.11-4.57)
	Year 3 (Hospital)	4	5	0.400 (0.08-1.86)				14	5	0.705 (0.33-1.57)
	Year 4 (Hospital)	18	9	1.000 (0.43-2.53)				8	9	1.401 (0.48-4.97)
	Year 5 (Hospital/SEP)	5	3	0.833 (0.16-5.37)				3	1	0.445 (0.15-1.30)
	Year 6 (Hospital)	NA	NA	NA				15	4	1.873 (0.60-7.75)
	Cumulative to date	**40**	**37**	**0.541 (0.34-0.87)**				**62**	**35**	**0.890 (.058-1.39)**
9-11 Years CYD 14 N=2618 CYD15 N=8436 CYD23/57 N=1311	Year 1 (Active)	5	5	0.502 (0.12-2.18)	2	8	0.125 (0.01-0.63)	3	2	0.759 (0.09-9.08)
	Year 2 (Active)	2	13	0.077 (0.01-0.34)	6	14	0.214 (0.07-0.59)	3	9	0.169 (0.03-0.68)
	Year 3 (Hospital)	6	3	1.009 (0.22-6.23)	10	9	0.554 (0.20-1.54)	3	5	0.308 (0.05-1.58)
	Year 4 (Hospital)	12	3	2.013 (0.54-11.11)	6	5	0.601 (0.15-2.49)	3	5	0.308 (0.05-1.58)
	Year 5 (Hospital/SEP)	3	2	0.755 (0.09-9.04)	1	1	0.498 (0.01-39.12)	1	3	0.171 (0.00-2.13)
	Year 6 (Hospital)	NA	NA	NA	NA	NA	NA	11	5	1.126 (0.36-4.14)
	Cumulative to date	**28**	**26**	**0.542 (0.31-0.96)**	**25**	**37**	**0.337 (0.19-0.58)**	**24**	**29**	**0.422 (0.24-0.75)**
12-16 Years CYD 14 N=2309 (up to 14) CYD15 N=10174	Year 1 (Active)	2	5	0.139 (0.02-1.22)	3	7	0.214 (0.04-0.94)	Not included in trial population		
	Year 2 (Active)	1	7	0.071 (0.00-0.55)	7	14	0.250 (0.09-0.66)			
	Year 3 (Hospital)	2	4	0.249 (0.02-1.74)	6	6	0.501 (0.13-1.87)			
	Year 4 (Hospital)	7	10	0.348 (0.11-1.01)	0	2	0.000 (0.00-2.67)			
	Year 5 (Hospital/SEP)	1	2	0.249 (0.00-4.79)	0	0	NC (NC)			
	Cumulative to date	**13**	**26**	**0.240 (0.11-0.48)**	**16**	**29**	**0.276 (0.14-0.52)**			

N= denominator of evaluable subjects for the RR calculation for the entire study.
SEP=Surveillance expansion phase

Consistent results were seen in those aged 4-5 in CYD23/57. In the 4-5 year age group, there were 5 hospitalized cases in Year 3 in the CYD group compared to 1 in the placebo group, a RR of 2.44 (95%CI 0.27-115.54). In Year 4, this excess was no longer apparent (5 cases in CYD group and 3 cases in the placebo group, a RR of 0.81 (95%CI 0.16-5.24), although in Year 5 there were 4 cases in the CYD group and 0 cases in the placebo group, and in Year 6 there were 11 cases in the CYD group and 4 cases in the placebo group.

In contrast, across older age groups (6-8, 9-11, and 12-16 years), an elevated risk was not seen consistently across the trials (Table 8). The relative risk point-estimate of hospitalized dengue was always below 1 in the ages included in the indication with two exceptions: in Year 4 of CYD14 for those first vaccinated aged 9-11 years, the relative risk was 2.013 (95%CI 0.54-11.11), and in Year 6 of CYD23/57 for those vaccinated at 9-11 years, the relative risk was 1.126 (95%CI 0.36-4.14). In comparison, the relative risk during Year 4 in the 9-11 year-olds in CYD15 was 0.601 (95%CI 0.15-2.49) and in CYD23/57 was 0.308 (95%CI 0.05-1.58). No Year 6 data are yet available from CYD14 or CYD15. In the older age groups, the relative risk over the full trial period to date (Years 1-5 in CYD 14 and CYD15, Years 1-6 in CYD23/57) was always statistically significantly protective. Based on a smoothing of vaccine efficacy by age performed by the manufacturer, the point-estimate of the relative risk for hospitalization due to dengue crosses 1.0 between 6 and 7 years of age and remains below 1.0; the 95% confidence interval remains above 1.0 until between 12 and 13 years of age (Figure 8). It should be noted these relative risk estimates are based on a small number of cases, and the relative risk estimates often change markedly with the addition/subtraction of even just 1 case.

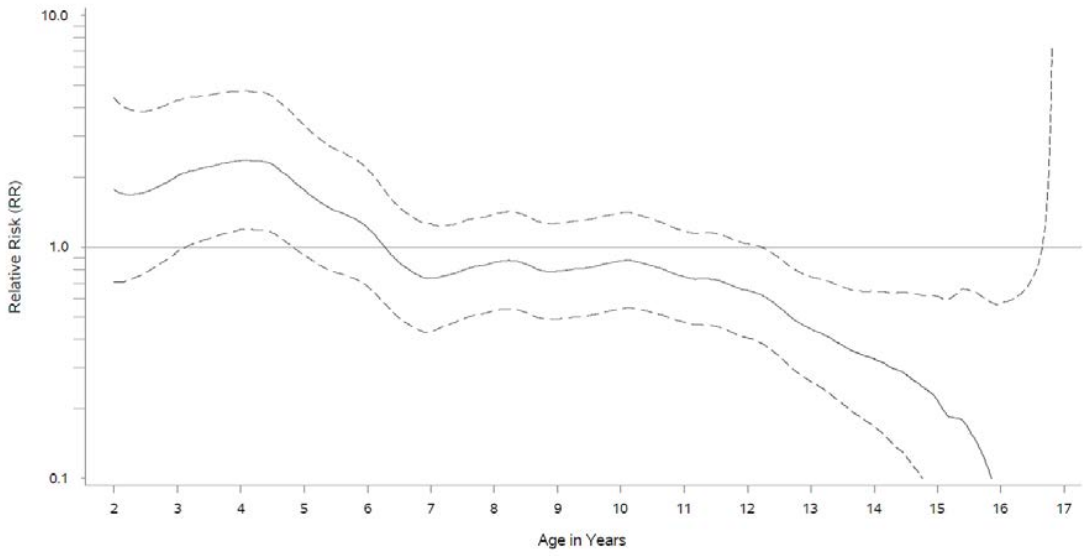
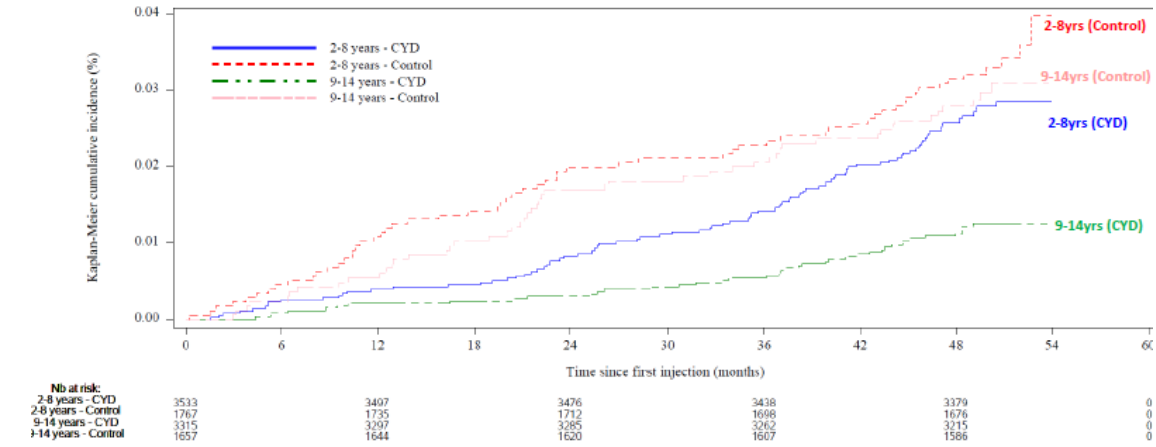


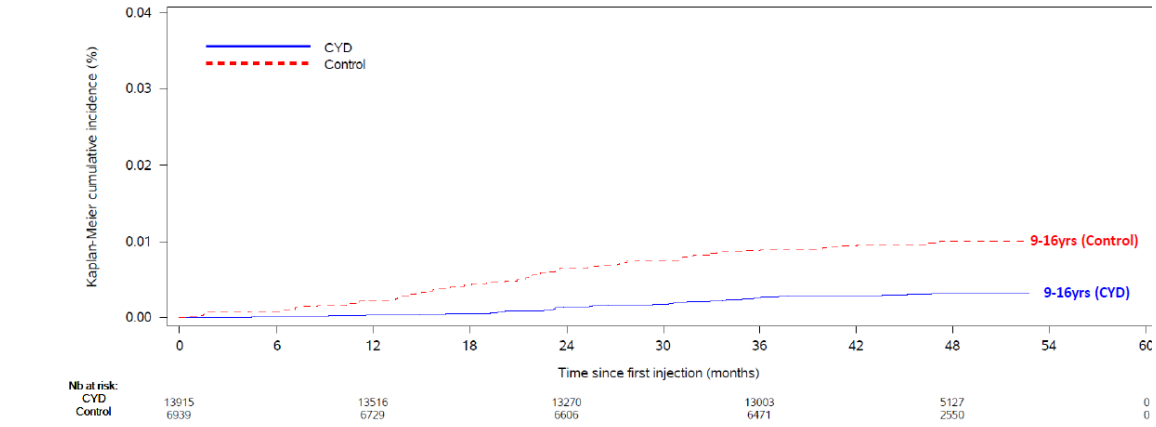
Figure 8 Relative risk (and 95%CI) against hospitalized symptomatic VCD in the Hospitalization Phase/Surveillance Expansion Phase due to any serotype by age in CYD14 and CYD15. Provided by the manufacturer on request.

In light of the signal that emerged in the 2-5 year age group, extensive profiling of these dengue cases was undertaken by the manufacturer. There was no apparent difference in the clinical severity of severe cases, either in the hospital phase compared to the active phase, or in the vaccinees compared to the controls [32]. There was no apparent difference in viraemia levels or cytokine profiles, including by age group, which has been argued to be counter to an immune enhancement hypothesis [36].

When considering 42 months of follow-up from the first dose, and an age stratification at 9 years, there is still an overall positive benefit overall in the CYD group 2-8 years of age (Figure 9). However, when further stratified by pre-existing age groups, the 2-5 year age group exhibits no benefit compared to the placebo group; the overall effect is negative, but does not reach statistical significance (Table 8).



A)



B)

Figure 9 Cumulative incidence of hospitalized VCD due to any serotype from first dose in A) CYD14 stratified by age groups, and B) CYD15 entire trial population. Provided by the manufacturer on request.

The Global Advisory Committee on Vaccine Safety (GACVS) reviewed longer-term follow up data through Year 3 of CYD14 and CYD15 [37]. GACVS noted the increased relative risk in the 2-5 year old population and highlighted the importance of understanding the potential factors associated with this signal that may be in addition to, or instead of, age. At the time of the data review, GACVS was unable to fully assess the risk in the youngest age group, currently excluded from the indication. GACVS emphasized the importance of further monitoring the risk of dengue requiring hospitalization (particularly severe dengue) in older individuals who are seronegative at the time of vaccination.

5.2 Severe dengue

A proportion of hospitalized dengue cases were classified as severe (IDMC definition). Due to the small numbers, case counts were combined over Years 1 and 2 (Active Phase) and Years 3-5 (Hospital Phase and Surveillance Expansion Phase) for CYD14 and CYD15 (Table 9). The results for severe dengue mirror those for hospitalized dengue. In the 2-5 year age group (2:1 randomization), in Years 1 and 2 there were 7 severe cases in the CYD group and 5 in the placebo group for a relative risk of 0.697 (95%CI 0.19-2.79). In Years 3-5, there were 13 severe cases in the CYD group and 1 case in the placebo group in Years 3-5 for a relative risk 6.473 (95%CI 0.97-275.1). In this age group, over the full trial period to date, there was a higher incidence in the

vaccinated group than in the placebo group, but the excess is not statistically significant. For the population above 9 years of age, the point estimates for relative risk against severe dengue were always below one with one exception in CYD14 (in the 9-11 year age group in Years 3-5, the relative risk of severe dengue was 3.525 (95%CI 0.45-158.86); this was not seen in CYD15 (relative risk 0.832, 95%CI 0.16-5.36) during the same time period). The point estimate of the cumulative relative risk over the full trial period to date was below 1 in the 6-8, 9-11, and 12-14 year age groups.

Table 9 Risk of severe (IDMC definition) hospitalized VCD by age group during full study period in CYD14 and CYD15. Provided by the manufacturer on request.

		CYD14			CYD15		
Age Group	**Time Period**	**CYD cases**	**Control cases**	**RR (95%CI)**	**CYD cases**	**Control cases**	**RR (95%CI)**
2-5 Years N=2451	Year 1-2 (Active)	7	5	0.697 (0.19-2.79)	Not included in trial population		
	Year 3-5 (Hospital/SEP)	13	1	6.473 (0.97-275.1)			
	Year 1-5	**20**	**6**	**1.660 (0.64-5.05)**			
6-8 Years N=2791	Year 1-2 (Active)	3	4	0.376 (0.06-0.22)	Not included in trial population		
	Year 3-5 (Hospital/SEP)	8	5	0.800 (0.23-3.11)			
	Year 1-5	**11**	**9**	**0.612 (0.23-1.67)**			
9-11 Years CYD14 N=2618 CYD15 N=8436	Year 1-2 (Active)	2	8	0.126 (0.01-0.63)	0	3	0.000 (0.00-1.21)
	Year 3-5 (Hospital/SEP)	7	1	3.525 (0.45-158.86)	5	3	0.832 (0.16-5.36)
	Year 1-5	**9**	**9**	**0.503 (0.18-1.43)**	**5**	**6**	**0.416 (0.10-1.64)**
12-14 Years CYD14 N=2309 CYD15 N=10174	Year 1-2 (Active)	0	3	0.000 (0.00-1.20)	1	8	0.062 (0.00-0.47)
	Year 3-5 (Hospital/SEP)	1	3	0.166 (0.00-2.07)	1	2	0.250 (0.00-4.81)
	Year 1-5	**1**	**6**	**0.083 (0.00-0.68)**	**2**	**10**	**0.100 (0.01-0.47)**

5.3 Potential explanations for signal in 2-5 year age group

The manufacturer has described interrelated working hypotheses as possible explanations for the signal seen [38]. The following is an excerpt from their paper:

> *The risk of developing severe disease is higher for individuals with a secondary heterotypic infection than for those with a primary infection. This may be mimicked by CYD-TDV vaccination of seronegative individuals, whereby vaccination represents a 'primary-like' infection dominated by one or a few serotypes, and diminishing responses lead to only short-term cross-protection. As cross-protection wanes (potentially rapidly, owing to low antibody titres), so vaccine efficacy is reduced, as discussed above. Furthermore, vaccinated individuals could be at greater risk of developing a severe or symptomatic 'secondary-like' infection the first time they contract DENV: the vaccine could act as their primary infection, and the subsequent true primary wild-type DENV infection (which would otherwise be typically less severe) could simulate a secondary wild-type infection (which is typically more severe).This situation is also more likely to occur in younger vaccinated individuals.[38]*

Related, the manufacturer has proposed three interrelated hypotheses, also described in the paper.

- Hypothesis 1: waning protection leads to reduced efficacy, particularly in seronegative individuals…*Humoral immunity is likely to wane more rapidly in seronegative than in seropositive vaccinated individuals, as the recall response in seropositive vaccinated individuals gives rise to a stronger immune response than is seen in their seronegative counterparts. Given that younger age groups have a higher chance of being seronegative than older age groups (as the likelihood of being exposed to a primary infection increases with age), waning immunity is more probable in the youngest vaccinated individuals. Consequently, their neutralizing responses are more likely to rapidly fall below protective thresholds for all four DENV serotypes and to present a monotypic pattern that is less likely to be cross-protective.*
- Hypothesis 2: younger vaccinated individuals are more susceptible to severe infection. *Age-related differences in vaccine efficacy may also be explained by differences in physiology that influence susceptibility to severe infection. For example, age differences at the microvascular and vascular levels could be associated with higher chances of plasma leakage, which is thought to contribute to severe disease. In addition, younger children could be less able to recover from dengue-induced disorders, increasing their chances of requiring hospitalization. Furthermore, some qualitative differences at the immunological level were seen between children 5–10 years of age and those who were older. These differences may affect innate immune responses, the diversity of the repertoire of B cells and T cells that are mobilized or the affinity of B cell clones, thus influencing the duration and quality of the CYD-TDV-induced specific responses in younger children versus older children. In agreement with there being an independent age effect, pooled efficacy analyses showed a significant vaccine efficacy in seronegative individuals 9 years of age or older, whereas the vaccine was not significantly effective in younger seronegative individuals.*
- Hypothesis 3: susceptibility in vaccinated individuals is temporally clustered. *The fact that vaccination of seronegative individuals may represent an attenuated subclinical primary infection means that in the efficacy trials, such a primary infection has been temporally clustered in vaccinated individuals. This clustering occurred in a short period of time because of the condensed enrolment periods of the trials, whereas subjects who received the placebo are exposed to a primary wild-type infection over a longer period of time. Therefore, differences in seasonality and endemicity may mean that the primary infection and the subsequent secondary exposure to a heterologous serotype (with a potentially more severe outcome) are more spread out in time for control subjects than for vaccinated individuals. As a consequence, during a given period of time, one would observe more dengue-related hospitalizations for vaccinated individuals than for controls; however, this imbalance may be only temporary, occurring during a limited period of time, after which more severe cases would be accrued in placebo recipients.*

The hypotheses will require further data and follow up time to lend support or refute. The diminishing relative risk in Years 4 and 5 in the 2-5 year age group in CYD14 may support to some extent the cluster hypothesis. For policy considerations, with the data currently available, a key question is whether individuals who are seronegative at vaccination but above 9 years of age could be at increased overall risk of hospitalized or severe dengue. A further consideration is whether, if there is an increased risk at certain periods after vaccination in this population, there is simply no overall benefit, early protection being balanced out by a later excess of cases among vaccinated, or whether there is overall harm. Current data do not show an increased risk on hospitalized or severe dengue at any time point in seronegatives over 9 years of age, although data are very limited by the number of cases of hospitalized and severe dengue that occurred in the immunogenicity subset, for which baseline serostatus was known.

5.4 Duration of Protection

Vaccine efficacy against VCD of any severity has been measured in Years 1-2. The Surveillance Expansion Phase, started in Years 4 and 5 in response to the increased risk seen in children 2-5 years of age in Year 3, will collect data on virologically-confirmed dengue of any severity. Thus, the ability to make inferences about duration of protection against dengue of any severity are currently limited, but will be informed by future data generated from the ongoing clinical trials.

Data on hospitalized dengue has been collected throughout the trial period, though with different surveillance systems in the Active and Hospital Phases. With the limitations of this change in surveillance and that the CYD and placebo groups have different histories of dengue exposure at the start of later time intervals, it is one source of data available now to assess protection over the period of the trial.

For hospitalized dengue in ages included in the indication (9-16 years), the point estimate of relative risk of hospitalized dengue remains below 1, suggesting a sustained protective effect (Table 8). The point estimates year-by-year are variable, although in many instances the point estimate becomes closer to 1 as time progresses. In all age groups, the relative risk of severe dengue among vaccinated compared to controls is lower during the Active Phase than during the Hospital Phase (Table 9). These data may suggest potential (though unconfirmed) waning protection across all age groups.

6. IMMUNOGENICITY

6.1 Immune response induced by CYD-TDV

CYD-TDV induces neutralizing antibodies against all 4 serotypes, as measured by $PRNT_{50}$. In seronegative vaccinees, responses to the 3-dose regimen are mostly homotypic, usually (but not exclusively) to DENV4, while responses to the other serotypes are largely based on cross-reactive antibodies ([38, 39]). T cell responses against structural antigens of DENV are also induced, as well as against non-structural antigens of the yellow fever vaccine virus. In vaccinees seropositive before vaccination, neutralizing antibodies titers are higher following vaccination (Figure 10 and Figure 11). Vaccination may boost previous natural immunity; responses due to vaccination are specific to the original infection serotype and cross-reactive against all serotypes as seen upon secondary wild type infection. Responses specific to other serotypes are also induced. A broader T cell response is also induced in seropositives compared to seronegatives. In addition, T cell responses against non-structural antigens of the dengue viruses are recalled in vaccinees seropositive before vaccination [40].

In multivariate regression analysis of phase 2 immunogenicity data from various trials in Latin America and South East Asia, two major predictors of post-vaccination titres were identified: baseline immune status (negative, mono-, multivalent) and trial location [41]. Age and gender were not predictors.

In the Phase 3 trials, GMT increased post-dose 2 (no post-dose 1 samples were taken), and did not increase post-dose 3 (Figure 10 and Figure 11). GMT were higher in those vaccinated who were seropositive at baseline compared to seronegative at baseline. GMT were higher in CYD15 compared to CYD14: in the CYD group (regardless of serostatus), GMT after dose 3 were 166, 355, 207, and 151 for serotypes 1, 2, 3, and 4, respectively, in CYD14 [30], and they were 395, 574, 508, and 241 for serotypes 1, 2, 3, and 4, respectively, in CYD15 [31]. It should be noted that baseline seropositivity, as well as age, was higher in CYD15 (79%) compared to CYD14 (68%) (Table 3).

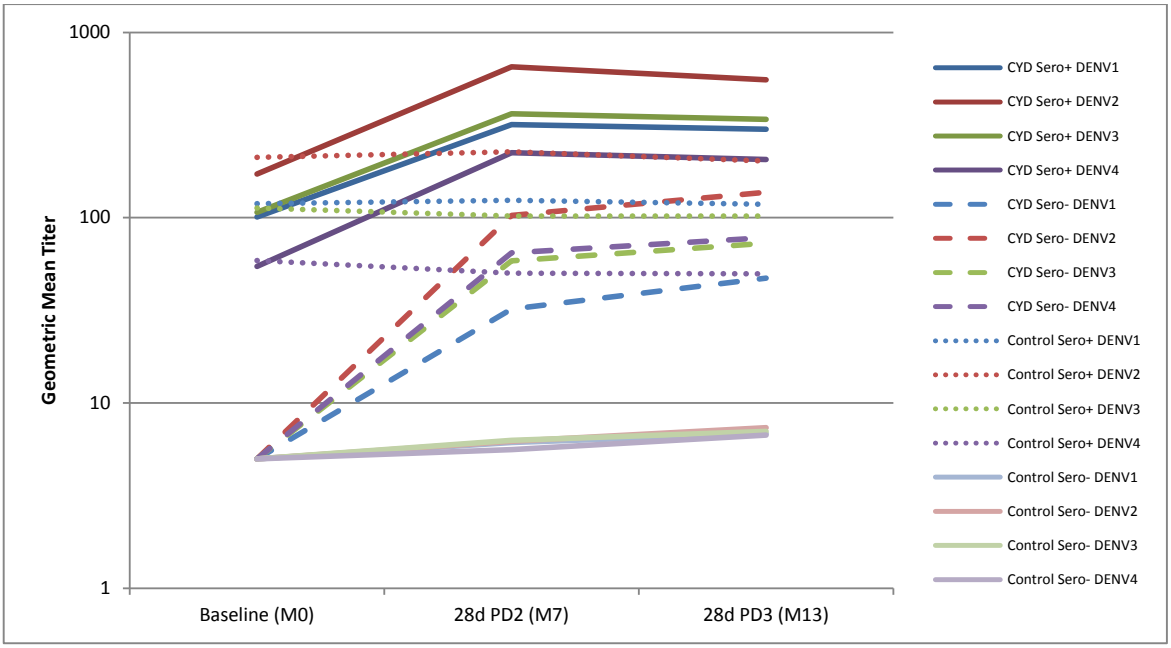


Figure 10 Geometric mean titers (GMT) as measured by PRNT50 in CYD14, by serostatus in CYD group (seropositive and seronegative combined in control group). Provided by the manufacturer on request.

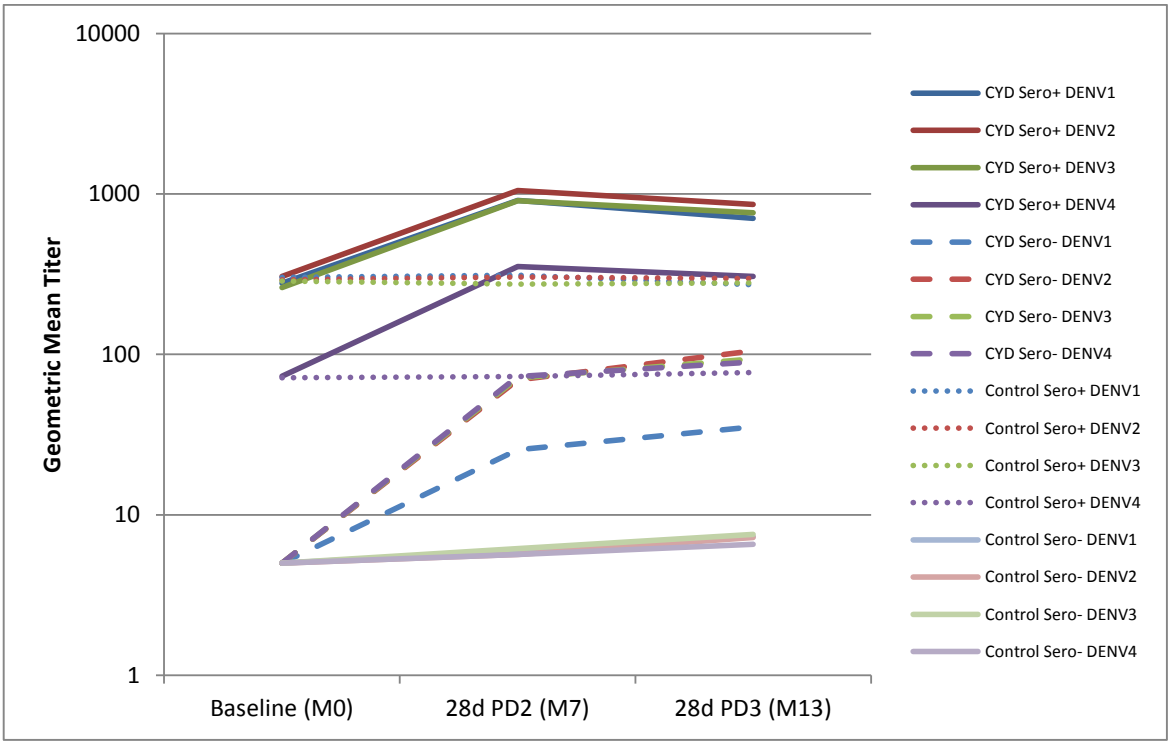


Figure 11 Geometric mean titers (GMT) as measured by PRNT50 in CYD15, by serostatus in CYD group (seropositive and seronegative combined in control group)[31] and manufacturer provided on request.

No correlate of protection for dengue has been established to date, although some correlation has been described between vaccine-induced neutralizing antibody titers and protection from VCD for a given serotype [42].

6.2 Immunologic rationale for vaccine schedule

Before vaccine efficacy data were available from the Phase 2b and Phase 3 trials, immunogenicity based on tetravalent seroconversion (in the absence of a correlate of protection) was an important factor in determining the number of doses to be included in the vaccination series. However, it is unclear how seroconversion, either against all four serotypes or fewer, relates to protection against disease.

Among subjects seropositive at baseline (to at least one serotype), many had a tetravalent response, even prior to receiving any vaccination, at baseline (Figure 12 and Figure 13). Following two doses, the majority of seropositive subjects had a tetravalent response in both trials. A subsequent dose increase the proportion of subjects with tetravalent responses. The range from studies in Latin America is smaller than in Asia, with, generally, a higher proportion for tetravalent responders in Latin America.

In seronegative subjects, the proportion with a tetravalent response by dose is lower than in the seropositive subjects. The 3-dose series again increased the proportion of subjects with a tetravalent response, although there was still a range across ages, with between 38% and 100% of subjects with a tetravalent response following three doses in the 18-45 year age group in Asia.

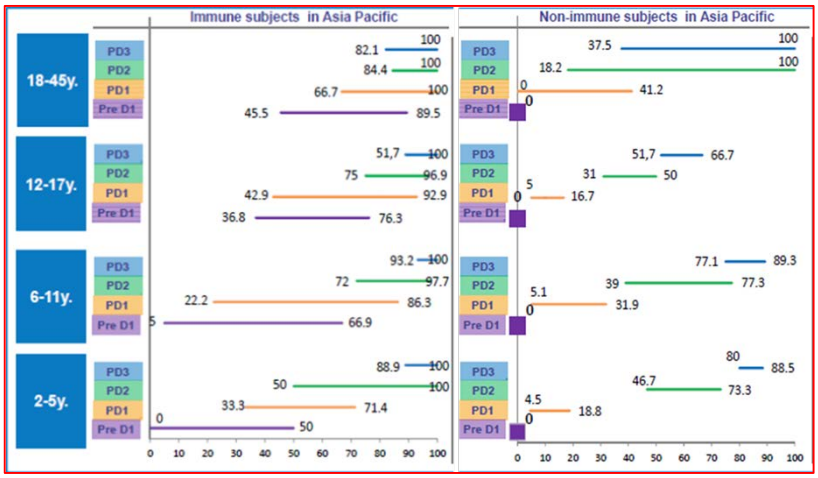


Figure 12 Range of percentage of subjects seroconverted to four serotypes ($PRNT_{50}\geq10$) by dose, age, and serostatus from Phase 2 trials in Asia. Provided by the manufacturer on request.

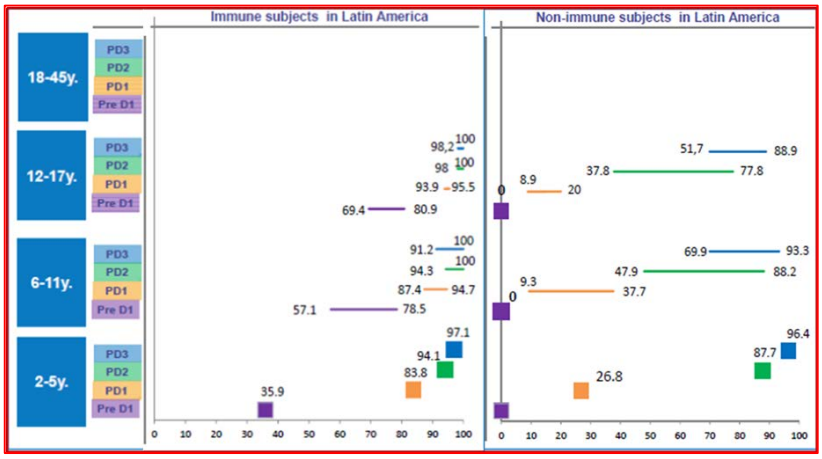


Figure 13 Range of percentage of subjects seroconverted to four serotypes ($PRNT_{50}\geq10$) by dose, age, and serostatus from Phase 2 trials in Latin America. Provided by the manufacturer on request.

Considerations of vaccine efficacy by dose were described in Section 4. While the vaccine efficacy estimates between doses were comparable to post-dose 3 vaccine efficacy estimates, these are pooled populations with about 70% seropositive subjects. Vaccine efficacy with fewer than 3 doses could vary by serostatus, as was seen after 3 doses.

6.3 Bridging vaccine efficacy beyond the age groups included in efficacy trials

At the time of writing, NRAs from the five countries that have registered the vaccine approved an indication in individuals 9-45 or 9-60 years of age, although vaccine efficacy data were available only up to 16 years of age. The age groups included in the efficacy trials were selected based on the high incidence. Safety and immunogenicity studies were undertaken in 294 individuals aged 18-45 in endemic settings (Table 1). Although there is no correlate of protection to be used for extrapolation, it has been shown that serostatus at baseline is associated both with age and with higher titers post vaccination. Comparing post-dose 3 titers from the vaccine efficacy studies to post-dose 3 titers from immunogenicity studies in Vietnam (N=20 aged 18-45) and India (N=126 aged 18-45), titers in adults in endemic settings were typically statistically significantly higher than in the older children and adolescent trial population (Sanofi Pasteur, personal communication). Given efficacy was established in this younger population, it was extrapolated that efficacy would also be similar or better in comparable adult populations.

6.4 Challenges interpreting immunogenicity data

Although neutralization antibodies are believed most likely to be a correlate of protection (as is the case for Japanese encephalitis, yellow fever and tick-borne encephalitis vaccines), limitations in the $PRNT_{50}$ assay and assumptions about needed titer levels for protection across 4 different serotypes make interpreting immunogenicity results difficult. With regards to the neutralization assay, there has been interassay and inter-laboratory variation demonstrated [43]. With additional variability induced by different of viral challenge strains and cell lines used, numerical values across vaccine developers/labs should be compared with caution. Even within a single laboratory, interassay variation may be as much as 2- or 3-fold different [44]. There is also cross-reactivity with other flaviviruses, making the characterization of an individual's flavivirus exposure history very difficult.

The traditional $PRNT_{50}$ is performed in Vero or LLC-MK2 cells, which do not include Fcγ receptors or produce antiviral interferon, in contrast to the human dengue target cells (i.e. monocytes, macrophages, and myeloid dendritic cells) [43]. The $PRNT_{50}$ assay also does not allow for differentiation between monotypic and heterotypic (temporarily cross-protective) antibodies, and may result in higher GMTs than in a different cell substrate more similar to the human *in vivo* experience. Until the first vaccine efficacy data were available in 2012, it was assumed that seroconversion would correlate with protection from disease. Although CYD-TDV induced a balanced antibody response by $PRNT_{50}$, vaccine efficacy by serotype varies. This could be due to qualitative differences in antibodies or potentially variable thresholds of antibody required to neutralize each dengue virus serotype. Depletion assays are useful to assess the relative contribution of monotypic and heterotypic responses across serotypes. New assays that address the limitations of the traditional $PRNT_{50}$, as well as a better understanding of the contribution of cellular immunity, will enhance the use of immunogenicity results in the absence of efficacy data to evaluate vaccine performance.

7. VACCINE SAFETY (NON-DENGUE)

7.1 Reactogenicity

Safety data across multiple studies that used the final formulation and final vaccination schedule have been pooled for the age range of 9-60 years, both in endemic and non-endemic areas. CYD was more reactogenic than placebo, although the percentage of subjects was comparable. Among solicited injection site reactions, the most common was pain, reported by 45.2% of subjects aged 18-60 years and 49.2% in subjects ages 9-17 years [45]. Of all solicited injection site reactions, less than 1% were Grade 3. Over 60% of participants reported a solicited systemic reaction, of which approximately 10% were Grade 3, most related to headache

and fever. The most common solicited systemic reactions were headache (>50%), malaise (>40%), and myalgia (>40%). Fever occurred in 5% and 16% of participants in the adults 18-60 and subjects 9-17, respectively. A review of safety outcomes by serostatus and by age group (9-17 years and 18-60 years) did not identify any signals of concern (data not shown).

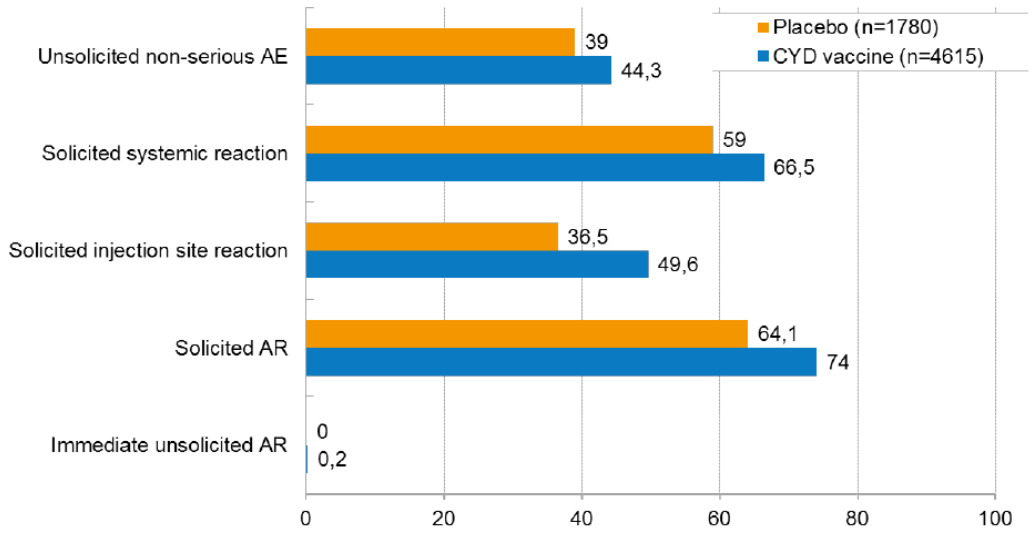


Figure 14 Percentage of subjects presenting with at least 1 reaction or event – subjects aged 9-60 years (pooled across multiple studies)[45].

Table 10 Percentage of participants in CYD14 and CYD15 experiencing safety outcomes [30, 31]. i.e. at least one SAE and death reported from baseline to month 25 (safety analysis set) and reactogenicity events reported within 28 days after any injection (subset analysis).

Adverse Health Outcome	CYD14 % (95%CI)		CYD15 % (95%CI)	
	CYD	Control	CYD	Control
SAE	5% (4.7-5.7)	6% (5.6-7.3)	4.1% (3.7-4.4)	4.4% (4.0-4.9)
Death	<1% (0.0-0.1)	0% (0.0-0.1)	<1% (TBC)	<1% (TBC)
Immediate unsolicited non-serious AEs	0% (0.0-0.3)	0% (0.0-0.6)	0.2% (0.0-0.7)	0.2% (0.0-0.8)
Solicited injection-site reaction	47% (44.8-50.2)	43% (39.2-46.9)	50.8% (48.1-53.6)	42.4% (38.6-46.3)
Solicited systemic reaction	57% (54.3-59.7)	55% (51.5-59.2)	68.4% (65.9-70.9)	69.5% (65.8-73.0)
Unsolicited non-serious AE	37% (34.1-39.3)	40% (36.7-44.3)	44.6% (41.9-47.4)	44.0% (40.2-47.8)
Unsolicited non-serious AR	1% (0.9-2.2)	<1% (0.3-2.0)	1.2% (0.7-1.9)	0.8% (0.2-1.7)
Unsolicited non-serious injection site AR	<1% (0.3-1.3)	<1% (0.0-1.1)	0.7% (0.3-1.3)	0.5% (0.1-1.3)
Unsolicited non-serious systemic AE	37% (34.1-39.3)	40% (36.7-44.3)	44.6% (41.9-47.4)	44.0% (40.2-47.8)
Unsolicited non-serious systemic AR	<1% (0.4-1.4)	<1% (0.2-1.5)	0.5% (0.2-1.1)	0.3% (0.0-1.1)

All but SAE and death are based on reactogenicity subset

No deaths were vaccine related. AE=adverse event. AR=adverse reaction. SAE=serious adverse event.

*Includes SAEs due to virologically confirmed dengue.

7.2 Serious adverse events

In the Phase 3 trials, the number of serious adverse events (SAEs) was similar between CYD and placebo group. Related SAEs up to 28 days after a CYD injection occurred in 6 subjects (headache and polymyalgia rheumatic in adults, and allergic urticaria, asthma, acute polyneuropathy, and tension headache in 9-17 year-old participants). An additional SAE was classified as related by the investigator in the 28 days to 6 months post CYD injection (blighted ovum), and 1 SAE of convulsion was judged to be related by the sponsor (not the Investigator).

7.3 Adverse events of special interest

The following adverse events of special interest (AESIs) have been defined by the manufacturer for CYD: allergic reactions within 7 days after vaccination, acute viscerotropic or neurotropic disease (AVD, AND) with 30 days after vaccination, and serious dengue disease at any time during the study.

No immediate anaphylactic shock has been reported post-vaccination. Five subjects receiving CYD have experienced a serious potential allergic reaction: 4 subjects with asthma/asthmatic crisis (all had medical history), and 1 urticaria (with history of allergic rhinitis). In the placebo group, there was one serious adverse event suggestive for allergic reaction (asthma in a subject with a history of asthma). There have been no confirmed AVD or AND cases in the studies. Severe dengue disease was discussed in Section 5.

7.4 Pregnancy

In the licensed indication, pregnancy and lactation are contraindications. A total of 613 pregnancies (402 in the CYD group and 211 in the placebo group) were reported from all CYD dengue vaccine trials (SP personal communication). They were mainly reported during CYD15. Among the 402 pregnancies reported in the CYD group, 22 pregnant women were inadvertently exposed to CYD-TDV (i.e. vaccinated 7 days after LMP or 7 days before estimation of conception or later during pregnancy). Of these, 17 resulted in a live birth, 1 resulted in an abortion (spontaneous and unspecified), 1 resulted in elective termination, 1 still birth, 1 death in utero, and 1 unknown. Of 211 pregnancies reported in the placebo group, 12 pregnant women were exposed, of which all 12 resulted in a live birth.

8. ESTIMATED VACCINE IMPACT

In April 2015 WHO initiated an open call for mathematical modellers to participate in a consortium called “Comparative modelling of dengue vaccine public health impact” (CMDVI). The purpose of the consortium was to generate model-based predictions of the potential population-level public health and economic impact of CYD-TDV, a primary goal of which was to inform SAGE recommendations on CYD-TDV. Eight modelling groups participated. The full results of this effort is an accompanying document (Flasche S. *et al*., Comparative modelling of dengue vaccine public health impact (CMDVI), SAGE Yellow Book).

The vaccine mode of action and introduction strategies were agreed to in collaboration with the SAGE Working Group in order to maximize relevance of CMDVI to SAGE deliberations. The models adopted, with small variations, the most parsimonious vaccine mode of action that matched the observed trial data; namely, that vaccination, similarly to natural infection, induces transient, heterologous protection against infection with any serotype. Furthermore vaccination acts like a silent natural infection in that a subsequent natural breakthrough infection in a vaccinated individual has the same pathogenicity as the latter of two natural infections in the same individual if she was unvaccinated. All results were generated for a range of transmission intensities, characterized by the proportion of 9 year olds that are seropositive (referred to as SP9, applied at seropositivity rates of 10%, 30%, 50%, 70% and 90%). Case definitions for symptomatic and hospitalized cases followed the clinical trial definitions.

All models predicted that routine vaccination of 9 year-olds with CYD-TDV at 80% vaccine coverage would cause an overall reduction in dengue disease in moderate to high transmission intensity settings (SP9≥50%). This range of transmission intensity covers all the sites selected for the phase 3 trials of CYD-TDV. The impact of vaccination was greatest in high transmission intensity settings (SP9≥70%), where the reduction in dengue-related hospitalizations predicted by the models ranged from 10% to 30%. Predicted impact on all symptomatic dengue disease were generally comparable to impact on hospitalised disease in these transmission settings.

Most models predicted that in very low transmission intensity settings (SP9=10%), vaccination was likely to increase dengue hospitalization rates. This was due to a key assumption used by the models, that vaccination primes seronegative recipients to have a 'secondary-like' infection when they are exposed for the first time, which thus can increase incidence of symptomatic and hospitalized dengue in low transmission settings. In the absence of vaccination, when transmission intensity is low, a high proportion of individuals never experience a natural secondary dengue infection.

In settings with slightly higher (but still low) transmission intensity (SP9=30%) there was less consensus between the predictions of different models; those models which better reproduced the risk increase in 2-5 year age group in the longer-term follow-up tended to predict that vaccination at age 9 years would increase hospitalizations in this setting, while other models predicted a beneficial effect of vaccination.

For all levels of transmission intensity, the predicted impact of vaccination scaled approximately linearly with the number of people vaccinated when different coverage levels were examined and when the potential impact of a catch-up campaign was explored.

All models predicted that as transmission intensity increased, the optimal age for routine vaccination decreased. Within the age range considered in the exercise (9-18y), vaccination at 9 years of age was optimal for the highest transmission intensity setting (SP9=90%). Vaccination at between 11 and 13 years of age was near-optimal for the SP9=70% setting for most models. The optimal age range increased to 14-18 years in the SP9=50% moderate transmission setting, and to 16-18 year olds for the SP9=30% low transmission intensity setting. All models predicted a positive impact on dengue disease in all settings with SP9≥30% if vaccination targeted children aged 14 years or older.

Vaccination was predicted to be potentially cost-effective in settings with SP9=30-90%, if the vaccine can be purchased and delivered cheaply enough. However, the results derived indicated that vaccination will only be cost-effective using the public payer perspective if the total cost of fully vaccinating one person is below $40 ($15 at SP9=30%). Given that the recurrent costs of delivering three doses of HPV vaccine in a similar age group in low and middle income countries lies in the range $1 - $16, this suggests that vaccination may not be cost-effective in the SP9=30% setting, and that the vaccine would have to be competitively priced and/or co-administered with other vaccines in higher transmission settings. Vaccination is more cost-effective if a societal perspective is adopted or a higher value is placed on averting a DALY. It should be noted, however, that the CMDVI results are only indicative and should not be used as a substitute for more targeted analyses to inform country-specific decisions.

9. PROGRAMMATIC CONSIDERATIONS

As part of the deliberations on the use of any new vaccine, the programmatic implications and operational feasibility of the proposed vaccination schedule are important issues to be considered. The following section outlines some of the programmatic considerations specific to the licensed dengue vaccine (indicated in several endemic countries for individuals 9-45 or 9-60 years of age living in endemic settings), drawing lessons from recent HPV vaccine introductions in adolescents as well as from routine infant immunization.

In the absence of a SAGE recommendation and WHO position, this section serves to provide some preliminary thoughts based on the knowledge and experience of immunization programme experts. If appropriate, a

broader consultative process with partners and country programmes will be undertaken to design and plan for the introduction of the CYD-TDV vaccine.

Recently, the EPI programmes in most countries have accumulated limited but significant experience with delivering injectable vaccines to individuals outside the traditional EPI age group of less than one year, including TT, HPV, rubella, Men A and seasonal influenza vaccines. The 0/6/12 month schedule of the CYD-TDV vaccine could pose a potential new challenge in some settings. Nonetheless, given the high awareness about dengue disease in affected countries (compared to awareness of the target condition for some other recently introduced vaccines), a dengue vaccine is more likely to lead to very high societal demand. As such, the efforts to overcome the delivery challenges listed above should be interpreted in this context.

9.1 Vaccine strategies

Serostatus: Based on the performance of CYD-TDV in clinical trials, the vaccine is more protective amongst individuals who have already been exposed to dengue infection than in those who are dengue non-immune (seronegative). There is a theoretical possibility that vaccination may be ineffective or may even increase the risk of severe and/or hospitalized dengue in those who are seronegative at the time of first vaccination, regardless of age. As a result, the greatest benefit would be expected in those who are seropositive at the time of vaccination. Currently, there is no rapid, point-of-care test to establish serostatus in order to allow for this kind of targeted vaccination. In the absence of ascertainment of serostatus at the time of vaccination, any use of the vaccine in a routine program would need to consider serostatus at the population level. Any requirement to conduct seroprevalence studies prior to vaccine implementation will be new to the EPI programme and will need careful communication to health workers as well as the general population.

Geographically targeted strategies: Given the dependency of vaccine performance on serostatus at baseline, as well as the heterogeneity in transmission intensity in small geographic areas, it is possible that subnational, localized vaccine introduction would be most cost-effective. This may lead to challenges in implementation if vaccination schedules are heterogeneous across districts or regions. Key considerations for a localized introduction should include population and health worker mobility, potential for disease to spread across initially defined boundaries over time (for example due to climatic changes and changes in vector prevalence/infection rate), public perceptions of inequity, as well as need for ongoing training of health workers as they move across districts. Individual countries can best assess their capacity for subnational introduction, including within political boundaries if appropriate.

Adding new vaccination contacts: The current schedule of the CYD-TDV candidate vaccine (0/6/12 months) will likely necessitate (an) additional vaccination contact(s) in most programmes. While HPV or TT-containing vaccines could be co-administered based on age indication, there are currently no co-administration data. Thus, countries may elect to stagger HPV and CYD-TDV, either requiring new vaccination visits or targeting different age groups during the same campaigns. Experience with new visits/school-based campaigns suggest substantial programmatic costs. Whether given at the health centre or through school-based campaigns, a three-dose vaccine given six months apart will require use of a vaccine registry maintained by the MOH and vaccination record for each vaccinee to ensure vaccinees receive all three doses. The majority of countries with dengue endemicity may need to build or strengthen such a tracking system.

Delivery strategy: Vaccination schedules targeting school age children and adolescents (e.g. 9-17 years) may be administered either through health facilities or through school-based programs. Both strategies have been effective at achieving high coverage of HPV vaccine in different settings. School-based delivery strategies will likely lead to high vaccination coverage when there is high school attendance and either a strong school health system or a strong collaboration between the ministries of health and education. In general, countries need to be aware that school-based programmes tend to be more costly than health-facility based strategies and require significant preparation and coordination with school authorities.

Similarly, health-facility based HPV vaccine delivery to school age adolescents has been successful in several countries and should be considered for dengue vaccine. In general, health facility based delivery in this age group has worked best in countries with fairly strong health systems, among other factors. WHO has produced a School Vaccination Readiness Assessment Tool to assist with planning and preparations.

Vaccination schedules targeted at adults or the out-of-school population would likely require alternate strategies. While some countries have some experience with influenza vaccine in adult populations, coverage rates are traditionally low. Countries would need to consider strategies to reach populations when there is not a ready platform (e.g. school health platform) and vaccination status would need to be carefully tracked to ensure compliance with the three-dose schedule.

Vaccine delivery through campaigns: Where the target age for the CYD-TDV vaccine is outside the school-age group, a possible option may be to deliver the vaccines through campaigns. Although many EPI programmes have significant experience with conducting large-scale and wide-age range campaigns with injectable vaccines (e.g. measles and Men A vaccines), there is limited experience with repeating such campaigns every six months. Other considerations for a campaign mode delivery include the added cost of *per diems* and other logistics, the additional trained manpower that may be needed, and the need to pay attention to how doses are recorded for individual vaccinees (especially those who may have missed the first or second waves of vaccination campaigns). Although the initial coverage may be high, with the build-up of new unvaccinated cohorts, issues of sustainability of the campaign approach will need to be addressed.

Integration with other interventions: Experience with the HPV vaccine has shown that new contacts with health care professionals during the adolescent period provide potential opportunities for integrating a variety of health interventions (e.g. sexual health, WASH, vision and dental assessments, tobacco counselling, menstrual hygiene, etc.). In practice, maximizing the potential value of such opportunities continues to be a challenge. Given the expected wide acceptability of a dengue vaccine, opportunities for integration with other health services and commodities should be sought at the onset. Experience suggests that for a successful integration, discussions among departments and ministries should commence as early as possible. It is important to note, however, that in situations where CYD-TDV is offered only to specific geographic locations, issues of equity and fairness with regard to the additional services/commodities will need to be addressed.

Vector control is an important intervention against all vector-borne diseases. There could be additive or synergistic effects when using vaccination and carefully implemented vector control together. Furthermore, community-based vector control interventions, such as COMBI (Communication for Behavioural Impact) and social mobilization for source reduction can serve as an opportunity to educate the public about vaccination. Furthermore, vaccination can serve as a platform to reinforce messages about community-based efforts.

Vaccine management and logistics: CYD-TDV is available both as a single- and multi-dose (5) vial. The multi-dose presentation requires less cold-chain capacity. However, per WHO recommendations [46], any reconstituted doses remaining at the end of the session would need to be discarded within 6 hours of opening/reconstitution or at the end of a session, whichever comes first. Although this is well-suited for vaccination campaign delivery (including school-based campaigns), multi-dose vials may lead to high wastage rates in the routine setting compared to a single-dose vial. On the other hand, single dose vials will require much greater cold-chain capacity, and the resource implications of expanding the cold chain should be given due considerations during the planning phase.

Coverage monitoring: Given the long interval between the first and final dose (12 months) and the need to ensure full vaccination with all three doses, countries will need to consider use of a vaccine registry maintained by the Ministry of Health and vaccination record for each vaccinee. Similarly, considerations for assessing the size of the target population for calculating administrative coverage will require careful review at the onset.

9.2 Co-administration

There are currently no data available from co-administration studies within the age indication for licensure from endemic settings, but three small co-administration studies were previously conducted in toddlers with YF, DTaP-IPV/Hib, and MMR. These studies were undertaken in Colombia/Peru, Mexico, and the Philippines, respectively. In adults, one study has been conducted in the US - a non-endemic setting (YF, different CYD schedule than sought for licensure). From these small studies it was concluded that there were no safety concerns (data were comparable when vaccines were co-administered or given alone), and that the immunogenicity profile was satisfactory both for CYD and for co-administered vaccines. The one exception to this was a lower response to serotype 4 in the study in US adults. In the labelling, there are no data with co-administration included because the toddler age group and non-endemic population are outside the first indication.

9.3 Outbreak response

CYD-TDV has not been evaluated in the context of a response to an identified outbreak. There are programmatic considerations for use in an outbreak response including factors such as size of the outbreak, timeliness possible of the response, population affected, transmission intensity and background serostatus of the target population, and programmatic capacity. Further discussion on the potential use in the context of an outbreak is provided in the proposed recommendations.

10. PLANNED POST-APPROVAL EVALUATION BY THE MANUFACTURER

The manufacturer has identified important potential risks (some basis for suspicion of an association with the product, but where association not confirmed): allergic reactions (including anaphylactic reactions, YF vaccine-associated viscerotropic disease and YF vaccine-associated neurotropic disease, increase in the severity of dengue disease from the start of vaccination, and waning protection against dengue disease over time.

Table 11 Summary of Risk Management Plan proposed by the manufacturer

Type	Activities
Post-marketing pharmacovigilance activities	• Routine pharmacovigilance monitoring • Enhanced safety surveillance
Long-term monitoring of ongoing efficacy studies	• Surveillance expansion in CYD14 and CYD15 (return to active surveillance currently in progress) • 5 year follow-up post-dose 3
Safety studies	• Background rates of conditions that can mimic viscerotropism and neurotropism • Cohort event monitoring (6 months after each dose, N=30,000, and an additional 3.5 years for SAEs) • Pregnancy registry
Effectiveness studies	• Community-based studies to evaluate impact on disease transmission • Facility-based studies to evaluate impact on hospitalization and severe dengue (with annual bleeding) • Monitor potential waning immunity over time
Additional clinical studies	• Booster studies • Clinical stable HIV+ subjects • Co-administration studies (HPV, Tdap)
Risk minimization	• Product information / labelling and packaging

CYD14 and CYD15 will be maintained for follow up until 5 years after the 3rd dose. Protocol amendments have been submitted for active surveillance to be re-instated (through SEP), which will allow for assessment of efficacy against VCD of any severity. Because blood samples will be taken at the time of re-enrolment, the relationship between dengue antibody level at that time and further subsequent VCD can be evaluated.

Vaccine schedules:

A study is planned to look at immunogenicity and safety in approximately 1,000 participants 9-50 years of age who receive either 1, 2, or 3 doses of the vaccine. A booster dose is also planned 12-24 months after the last dose (NCT 02628444).

Co-Administration:

Two co-administration studies have been identified as high priority given the indicated age range: HPV (tetravalent and bivalent) and Tdap. These are planned as Phase 3b, open-label, observer-masked studies and will assess the impact of co-administration on immunogenicity of each vaccine, as well as safety and reactogenicity.

Booster dose:

A multicentre study is planned that capitalizes on vaccinated recipients from previous Phase 1 and Phase 2 trials. Following the primary series of CYD-TDV, a 4-5 year gap will have occurred between the primary series of CYD-TDV and a single booster dose of CYD-TDV or placebo. There will be no comparison with age-matched subjects who have not received the primary series previously. Non-inferiority will be assessed, as will there be qualitative assessments of the immune response, and safety will be assessed (NCT02623725). Durability of the immune response up to 2 years post-booster will also be assessed.

11. OVERALL ASSESSMENT AND KEY RECOMMENDATIONS FOR SAGE CONSIDERATION

The first dengue vaccine has been thoroughly evaluated in two Phase 3 trials in Asia and Latin America and NRAs from several endemic countries have licensed the vaccine. The indicated age range for the vaccine based on current regulatory approvals is 9-45 years or 9-60 years. The trials were executed to a very high quality and the sponsor has proactively shared key results to allow for a robust assessment of the vaccine. Because there were two comparable large Phase 3 trials as well as the Phase 2b trial, it is possible to look for consistencies and differences. Vaccine effects during the Hospital Phase were based on relatively small numbers of hospitalized and severe cases, and thus these comparisons are particularly useful when there is a suggestion of a year-to-year aberration in one of the trials. When an unfavourable relative risk was seen, it was valuable to compare effects in the other two trials.

11.1 Assessment of vaccine efficacy and vaccine schedule

The primary endpoints were met in both Phase 3 trials. At a population level, the vaccine confers partial protection against virologically-confirmed dengue of any serotype. Secondary and exploratory analyses demonstrated vaccine efficacy in the first 25 months after the first dose is higher against serotypes 3 and 4 than against serotypes 1 and 2, vaccine efficacy is higher against severe and hospitalized dengue, vaccine efficacy is higher among older trial participants, and vaccine efficacy is higher amongst those who had already been exposed to dengue prior to vaccination.

Vaccine efficacy estimates produced in the trials represent averages over different ages and countries, which includes variable year-to-year dengue transmission, variable serotype transmission, and variable participant characteristics, including serostatus at baseline. Vaccine efficacy varied by country, probably due, at least in

part, to variations in these factors, and suggests that impact can be optimized in settings defined by key characteristics.

Importantly, the protection conferred by CYD-TDV was substantially higher among trial participants who were seropositive at the time of vaccination. Among trial participants included in the indication (9-16 years), vaccine efficacy among seropositives was 81.9% (95%CI 67.2-90.0), and vaccine efficacy in seronegatives was 52.5% (5.9-76.1). In seropositive individuals, there is a clear and important benefit against dengue of any severity. The strong effect seen in seropositives may be because the vaccine acts as a booster (or silent post-primary infection) that elicits broadly cross-reactive neutralizing antibodies against all serotypes, just as is seen with natural infection. In seronegatives, the lower bound of the 95% confidence interval was above 0, though the wide confidence interval, low GMTs, and suggestions of waning call into question whether there is any substantial cumulative benefit in this group.

While it would be preferable to target vaccination in those who are seropositive, appropriate point-of-care tests do not exist at this time, and thus age and the history of dengue in the target communities will need to serve as surrogate measures for vaccinating those who will benefit most from vaccination. The optimal age group will reflect the underlying disease transmission, with the goal for a majority of those vaccinated to be seropositive at the time of vaccination. If a majority of vaccine recipients are expected to be seropositive at vaccination, given the high incidence of dengue, the impact could be substantial in terms of absolute numbers of cases averted.

A 3-dose schedule given 6 months apart is not optimal from a programmatic perspective; however, high compliance with this schedule was achieved in the trials and experience gained with vaccine delivery for older children and adolescents indicates that it is likely to be possible to deliver a vaccine on this schedule to the 9-11 year age group, and likely to older school-age children as well (acknowledging drop-out rates increase with age). Phase 3 trial data suggest protection from the vaccine begins with the first dose. However, due to the high course completion rate in the trial, it is not possible within the trial to look at efficacy by doses received during the 25 follow up period, other than in the 6 months following each dose. Furthermore, whether the duration of protection is affected by the number of doses received also not known. Based on immunogenicity data, it is clear that the immune response in seronegatives is improved with doses 2 and 3. Therefore, until additional data are available on fewer than three doses through vaccine effectiveness studies, or until an immune correlate of protection is available, the protection seen in the trial can only be assured through use of a 3-dose schedule. Additionally, host factors such as serostatus will need to be considered in dosing regimens, as different schedules may protect some individuals but not others.

11.2 Assessment of risk of hospitalized and severe dengue over time and duration of protection

In the ages included in the indication, there was protection against hospitalized and severe dengue across the Phase 3 trials and up to the latest available follow up data (Year 5). The relative risks generated during the course of the Phase 3 trials were used as a safety endpoint, not an efficacy endpoint. However, there is evidence that the relative risks of hospitalized and severe dengue among those vaccinated moved closer towards 1 in years 3-5 compared with years 1-2, potentially indicating waning immunity (Table 9). Data generated in Year 5 with the Surveillance Expansion Phase will allow for comparison of vaccine efficacy against virologically-confirmed dengue generated in Years 1 and 2. When these data become available, potential waning immunity and booster needs can be better assessed, as can the overall benefit anticipated over time from vaccination.

An increased risk of hospitalized and severe dengue was seen in the 3rd year of follow up in 2-5 year-olds in CYD14. This increased risk was large (7.45 in Year 3), but diminished in Years 4 and 5. The Phase 2b trial in Thailand, CYD23/57, found similar effects. It could not be evaluated in CYD15 due to the absence of this age group in the trial. The 2-5 year age group also has the highest proportion of seronegatives. Thus, a key

question is to what extent the increased risk seen in the 2-5 year age group is due to age, serostatus, or a combination of the two. Looking across the trials in the older age groups, there was a lack evidence of an increased risk at any point during follow up. Only in the 9-11 year age group in CYD14 was a relative risk above one in Years 4 of follow up; however, as the relative risk was below 1 in this same age group in CYD15 and CYD23/57, it is not interpreted as a signal.

There are few data to support or refute any risk in seronegatives greater than 9 years of age. In CYD 14 and CYD15, over 70% of the population in this age group was seropositive, and this increased with age up to 16 years. The relative risks were below 1 over time in this age group (of both seropositives and seronegatives). Within the immunogenicity subset, among seronegatives, there is no indication that the same effect is observed in the 9-16 year-olds as was seen in the younger age groups. Current data are compatible with no reduction in disease risk among vaccinated seronegatives. However, it cannot be excluded that in the years following vaccination, seronegatives may be at an increased risk of dengue. Of note, there is a theoretical risk even in seropositives that as immunity wanes, they could too be at increased risk of severe and hospitalized dengue some years in the future.

The explanation for these findings in the 2-5 year age group is unclear based on available data. The hypotheses put forward by the Sponsor (Section 5.3) are plausible, in particular the suggestion that the immunological mode of action of the vaccine is to move individuals along the infection line. The clustering hypothesis may also help explain the initial elevated relative risk 7.45 in Year 3 that diminished to 1.4-1.5 with further follow-up. An age effect independent of serostatus, which would reduce the theoretical risk of predisposing older seronegative vaccinees to more severe forms of dengue, would also be compatible with the available data but requires further investigation.

11.3 Assessment of impact predicted by mathematical modelling

The positive benefit of vaccination provided in moderate-to-hight transmission settings of seroprevalence at 9 years of age of 50% or higher across 8 different mathematical models provides reassurance that use of the vaccine in these contexts will result in a population-level reduction in dengue, including for hospitalizations, which present an important burden on the health system. A reduction of 10-30% in dengue-hospitalizations was predicted over 30 years. Notably, impact was highest in transmission settings of 70% or higher seroprevalence at age 9 years. The variability in model outputs at low and very low transmission settings urges some caution in vaccine use in such settings. Importantly, these are population-level outputs that do not directly reflect individual-level effects, i.e. individual risk of hospitalized or severe dengue among vaccinated seronegatives, and some models do predict negative impact among seronegatives even in the 50% seropositivity setting (because in this transmission setting in the absence of vaccination, many seronegatives would not have experienced two dengue infections in their lifetime). However, additional data and follow up are needed to better characterize this risk in seronegatives in this age group to better understand the risk profile.

The optimal ages for vaccination vary by transmission setting; 9 years of age is only optimal in the highest transmission settings from the perspective of disease impact, although there may be programmatic reasons why 9 years of age may be preferable in settings with lower than 90% seropositivity in this age group. Impact variability by age was not substantial in the moderate (SP9=50%) to high (SP9=70%) transmission settings.

With the introductions scenarios modelled, which were chosen to be realistic in representing what most countries would consider, neither catch-up vaccination nor higher coverage in a routine program impacted transmission (i.e. little or no indirect effects). Cost-effectiveness analyses, evaluated using the CMDVI settings that were not country-specific, suggest that vaccination could be potentially cost-effective in moderate-to-high transmission settings, if the vaccine can be purchased and delivered cheaply enough. Importantly, country-specific analyses will be needed to assess cost-effectiveness with locally relevant parameters

The modelling comparison is an important tool to translate point-estimates generated from the trial, which varied by infecting serotype, age, serostatus, and severity, into predicted program impact. While there was a high level of consistency across the models, there are a number of uncertainties in the model assumptions, including how the mode of action of vaccination and duration of protection, which may vary by factors such as serostatus, that remain unknown. Empirical data remain critical. Modelling predictions will continue to be important tools as they are informed by newly generated data that address key remaining questions with respect to vaccine performance.

11.4 Assessment on other aspects of vaccine safety

Data from Phase 2 and Phase 3 trials have not signalled any safety concern other than the dengue-related signal described above. With regard to traditional safety considerations (reactogenicity, serious adverse events, etc.), CYD-TDV is well-tolerated. Due to the hypothetical risk of AVD and AND, the sponsor identified these events as adverse events of special interest and has initiated studies to assess background rates of AVD/AND-like disease, followed by post-licensure cohort event monitoring. Spontaneous reporting should also emphasize these outcomes to help assess whether there is any risk. The licensed Japanese encephalitis vaccine using the same ChimeriVax technology, IMOJEV, is similarly being evaluated, with no signal to date.

11.5 CYD-TDV in the context of the dengue control program

Vector control is the backbone of dengue control programs. CYD-TDV is a partially efficacious vaccine and vector control must remain a critical component of dengue control programs. Furthermore, the mosquito vectors of dengue transmit other important viruses, including Yellow Fever, Chikungunya, and Zika virus. Vaccination should be viewed as part of an integrated strategy to control dengue.

There are a number of strategies employed by control programs to reduce mosquito populations, and designing a dengue control program that optimizes allocation of resources is a priority. Many vector control interventions have been shown to be effective against entomologic indicators. However, given the lack of an established correlation between entomologic indices and epidemiologic outcomes, dengue control programs could be improved through the better evaluation of vector control and its effect on dengue disease. Vector control is a key strategy, but maintenance of a sustained impact of this intervention is a concern. Therefore, vaccination as a complementary to vector control will further strengthen dengue control programme in the countries

Countries will need to make decisions about vaccine introduction and use based on their own epidemiological setting and local resources and priorities. Given the complexity of the disease and the vaccine performance in different populations, mathematical models are a useful tool to predict potential impact of a vaccination program with local considerations. Additional work in developing modelling tools using local data that can be reasonably attained would assist in designing country immunization strategies.

11.6 Post-licensure data needs

The sponsor has submitted to NRAs a global Risk Management Plan to address a number key issues, including vaccine effectiveness, co-administration and booster needs, and traditional vaccine safety monitoring. NRAs have accepted this RMP. In addition, countries that introduce the vaccine need to conduct their own post-licensure monitoring and evaluation. It is important to bear in mind that, when considering empirical data for evaluating vaccine impact at the population level, dengue transmission is often highly variable year-to-year: a 20% change in dengue in either direction is within expected year-to-year variation. Policy-makers should be careful when interpreting surveillance data to infer vaccine impact or its absence.

One important research question remains that will not be adequately addressed in the RMP, which is to understand vaccine effects in individuals in the indicated age range who are seronegative at vaccination. There are different approaches that might be taken to evaluate risk in seronegatives; further consideration should be given to assess this hypothetical risk in parallel to vaccine introduction. Targeted studies in parallel to implementation are needed to answer this question definitively, otherwise it will remain a controversial issue and could compromise public confidence in the vaccine program.

11.7 Key conclusions and recommendations for SAGE consideration

Countries should consider introduction of CYD-TDV in geographic settings (national or subnational) with high dengue transmission, i.e. seroprevalence of approximately 70% or greater in the age group targeted for vaccination but not below 50%.[5]

Where possible, assessment of dengue transmission intensity should be supported by geographically relevant seroprevalence studies. Seroprevalence estimates should guide decision-making and introduction at subnational levels while noting that these are not precise indicators. Work is needed to identify routinely collected epidemiologic indicators that can be used to infer likely seroprevalence.

Decisions about introduction require careful assessment at the country level, including consideration of local priorities, subnational dengue epidemiology, predicted impact and cost-effectiveness with country-specific hospitalization rates and costs, as well as affordability and budget impact. Vaccination should be considered as an integrated strategy together with well-executed and sustained vector control and the best evidence-based clinical care for all patients with dengue.

CYD-TDV is recommended as a three dose series given 6 months apart. While protection has been documented after administration of the first dose, completion of the three-dose scheduled is recommended to assure the protection demonstrated in the 5-year period of trial follow up so far. Should a vaccine dose be delayed for any reason, it is not necessary to restart the course and the next dose in the series should be administered. Because of the duration of the vaccine schedule and to enable better vaccine monitoring, countries should have systems in place for tracking vaccination.

The target age for routine vaccination should be defined by each country based on an assessment of dengue endemicity and programmatic feasibility of targeting particular ages. The age to target to optimize impact likely varies by transmission setting.[6] Although only immunogenicity (not vaccine efficacy) has been studied in clinical trials of 17-45 year-olds, in principle these age groups could be targeted for vaccination. At this stage, insufficient data are available to permit a recommendation for use above the age of 45 years. No vaccination is recommended under age 9 years due to the potential safety concern signalled in children aged 2-5 years of age in the Phase 3 trial.

Risk of dengue hospitalization has been monitored for up to 4 years post-dose 3 in the Phase 3 trials. In the age group currently part of the indication (9-16 years), there is evidence of decreasing protection against dengue hospitalization over this time period. Ongoing follow up from the Phase 3 trials will provide information on the duration of protection, and it is possible that booster doses may be necessary to maintain protection. Currently there is no recommendation for a 4th dose.

[5] Mathematical modelling suggests optimal public health and economic impact in these transmission settings. Seroprevalence of 50% was at the lower end of the range of participants in Phase 3 trial sites. The overall seroprevalence in 9-16 year-old trial participants in the Phase 3 studies was approximately 80%. Modelling cautions against CYD-TDV use in lower transmission settings in early adolescence.

[6] Mathematical modelling found 9 years of age was optimal only in very high transmission settings (seroprevalence of 90% in that age group). In other settings with moderate to high transmission, vaccination between 11 and 13 years is predicted to maximize impact, although the variability in impact with age of vaccination was not great.

Co-administration is not recommended until data are available on the safety and immunogenicity of CYD-TDV when co-administered with other age-appropriate vaccines.

CYD-TDV should be introduced as part of a routine immunization program in appropriate settings. Catch-up campaigns targeting priority age groups defined by local epidemiology can be considered for a greater immediate impact. While adding age cohorts will give progressively better disease control, mathematical modelling of catch-up campaigns in 10-17 year-olds does not suggest a significant impact on dengue transmission (i.e. herd immunity). Future research will study a possible impact of the vaccine delivered through the routine system plus catch up on disease transmission.

Outbreak response

CYD-TDV should not be considered as a tool for outbreak response. A dengue outbreak is a signal that an improved dengue control strategy is needed. When an outbreak occurs in an area that meets the criteria for routine introduction in relation to transmission intensity, vaccination with the 3-dose schedule as part of an overall dengue control strategy may be considered.

Special populations

Pregnant women: CYD-TDV is contraindicated in pregnant and lactating women because insufficient data have so far been gathered on its use in pregnancy. However, based on limited data generated from inadvertent pregnancies that occurred during clinical trials, there are no data to warrant termination of an inadvertent pregnancy should the vaccination have occurred anytime during pregnancy. If a woman becomes pregnant before all three doses have been administered, the remaining doses should be administered after lactation.

Immunocompromised: CYD-TDV is contraindicated in immunocompromised individuals. More data will be available from upcoming studies in HIV-infected individuals.

Travellers: CYD-TDV has not formally been licensed for use in travellers. In travellers who have already been previously infected with dengue, vaccination for travel to high transmission settings may be beneficial. Extrapolation of data from the Phase 3 trials suggests that in such persons there may be some protection after the first dose, but completion of the full 3-dose schedule is still recommended. In travellers unlikely to have already had dengue, vaccination may be substantially less beneficial (and there is a theoretical risk that it may be harmful), analogous to seronegative individuals living in endemic settings. Co-administration with other travel vaccines is not recommended.

Health care workers: There are no specific recommendations for health care workers.

Surveillance

Dengue surveillance should be strengthened, particularly in the context of emerging infections with clinical similarities to dengue. In areas of the world for which there is a paucity of data, further characterization of the burden of dengue, which appears to be growing, is needed. Harmonized case-definitions are encouraged to enhance data sharing and comparisons across regions.

Using surveillance data to monitor population impact of a vaccination program may be challenging as the year-to-year variability in dengue transmission may be greater than the expected vaccine impact. Long-term monitoring for severe dengue in vaccinated subjects to assess long-term effects of vaccination should be done in selected areas.

Other aspects

Due to the partial efficacy of the vaccine against dengue of any severity, careful communication is needed to inform vaccinees that they may still be at risk of dengue and of the importance of receiving all three doses and of adhering to other disease preventive measures.

An assessment of vaccine effectiveness, and the durability of that effectiveness, with fewer than 3 doses is a priority. Current data suggest substantially lower benefit of vaccination in seronegative individuals 9-45 years of age. There is a theoretical possibility that vaccination could do harm in this population. Although theoretical risks not supported by data should not impede rollout of this vaccine, it is critical to evaluate as soon as possible whether there is any risk to this population.

Research Priorities

Table 12 Research priorities related to CYD-TDV identified by the SAGE Working Group on Dengue Vaccines

CYD Research Question	Priority	Addressed in RMP?	Notes
Risk of severe/hospitalized dengue over time in vaccinated seronegatives	**Critical**	Post-licensure studies in RMP will not test serostatus at the time of vaccination, although serostatus from yearly surveys will be known.	This is a critical research question that needs to be addressed with carefully considered research protocols. Dedicated studies are needed.
Duration of protection / need for additional doses	**Critical**	CYD14 and CYD15 long-term follow up will inform duration of protection, and booster dose studies are planned by the manufacturer.	Post-licensure monitoring will need to contribute to follow up for time periods beyond the 6 years planned in the clinical trials.
Vaccine effectiveness with fewer than three doses	High	VE studies are included in RMP.	
Dosing requirements by serostatus	High	Post-licensure studies in RMP will not test serostatus at the time of vaccination.	Different dosing schedules may be warranted for seronegative vs. seropositive subjects at baseline. Until a POC test is available, a single schedule that optimizes vaccine performance in all groups should be used. Dedicated studies are needed.
Co-administration with age-appropriate vaccines	High	Co-administration studies are planned by the manufacturer.	
Health impact assessment of vaccination program	High	Planned as part of RMP.	
Long-term transmission dynamics (serotype/ genotype selection)	High	No: out of scope of RMP.	As seen for other vaccine preventable diseases, serotype replacement is a real risk and should be monitored. Dedicated studies are needed.
Development of simple mathematical modelling tools for country use in decision-making with consideration of the local context.	High	No: out of scope of RMP.	Dedicated efforts are needed.

Table 13 Research priorities for the dengue field identified by the SAGE Working Group on Dengue Vaccines

General Research Areas	Priority	Notes
Second-generation vaccines that include characteristics such as improved protection against all four dengue serotypes, single-dose, for use in younger age groups	**Critical**	Dedicated studies are needed.
Immune correlate of protection	High	Broader efforts that could potentially be extrapolated to other/all dengue vaccines are needed. Dedicated studies are needed.
Improved POC diagnostics to identify seropositive/ seronegative individuals	High	Dedicated studies are needed.
Optimal integrated dengue control strategy (vector control strategies together with vaccination for maximum public health impact)	High	Dedicated studies are needed to understand the effectiveness of vector control and optimal integrated strategies.
Development of simple mathematical modelling tools for country use in decision-making with consideration of the local context.	High	Dedicated efforts are needed.
Research on burden of dengue in Africa	High	Dedicated studies are needed.

12. ACKNOWLEDGEMENTS

The Working Group would like to acknowledge the openness and responsiveness of the manufacturer in providing data requested and identified by the Working Group to be important for global recommendations. The Working Group would also like to acknowledge the contributions of the comparative modelling of dengue public health vaccine impact (CMDVI) modelling groups and WHO consultants for their collaboration and inputs.

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APPENDIX 1. SAGE WORKING GROUP ON DENGUE VACCINES MEMBERSHIP

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 (resigned from Working Group 29 February 2016)
- Alan Barrett, University of Texas Medical Branch, USA
- Anna Durbin, Johns Hopkins Bloomberg School of Public Health, USA (resigned from Working Group 31 December 2015)
- Elizabeth Ferdinand, University of the West Indies, Barbados
- Maria Guzman, Pedro Kouri Tropical Medicine Institute, Cuba
- 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 (resigned from Working Group 1 February 2016)
- Stephen Thomas, Walter Reed Army Institute of Research, USA

WHO secretariat

- Joachim Hombach
- Kirsten Vannice

Declaration of interests

All members completed a declaration of interests. Six members reported any relevant interests. It was concluded that all members could take part in full in all of the discussions. The reported relevant interests are summarized below:

Terence Nolan

- He received consultancy fees for participating in meetings and for data analysis and interpretation as member of Data and Safety Monitoring Board (DSMB) and Independent Data Monitoring Committee (IDMC) on Human Papilloma Virus vaccine from GSK. The consultancy was ceased by the 17th October 2012. This interest was assessed as personal, non-specific and financially significant*.
- In the time from 2008-2012 his institution received research support for vaccine trials implemented in Australia from a number of companies (including GSK, Wyeth, Novartis Vaccines, sanofi pasteur and CSL Ltd).These trials concern a number of vaccines (MenACWY, MenB, MenC, HibMenC Adult and peadiatric TIV, H1N1 and H5N1 vaccine and DTPa-Hib-hepB-IPV-MenC vaccine). This interest was assessed as non-personal, non-specific and financially significant*.
- His institution receives research support to conduct a follow-up clinical trial on a birthdose of Pertussis Vaccination from GSK. This interest was assessed as non-personal, non-specific and financially significant*.

- His institution receives research support to conduct a Meningococcal ACWY vaccine clinical trial from GSK. This interest was assessed as non-personal, non-specific and financially significant*.
- He serves as principal investigator for a clinical trial assessing the antibody response and persistence following MenACWY-TT funded by GSK and Murdoch Childrens Research Institute. This interest was assessed as personal, non-specific and financially significant*.

Piyanit Tharmaphornpilas

- She received in 2011 a travel grant from a joint venture of the Thai Government Pharmaceutical Organization - Merieux Biological Product to attend the Re-invigorating Immunization Policy Implementation and Success: From Parent to Partner and from Broad to Engagement. This interest was assessed as personal, non-specific and financially significant*.

Alan Barrett

- His institution holds a contract funded by the U.S. National Institutes of Health to conduct a phase I clinical trial of the Takeda dengue vaccine candidate. This interest was assessed as non-personal, specific, and financially significant*.
- His institution participates in collaborative projects with Hawaii Biotech/Merck, two of which study recombinant flavivirus immunogens (tick-borne encephalitis). This interest was assessed as non-personal, non-specific, and financially significant*.
- He is co-investigator of a contract funded by the U.S. National Institutes of Health to test dengue drugs and vaccines in mouse models. This interest was assessed as personal, specific, and financially significant*.

Anna Durbin (resigned from Working Group in December 2015)

- She is co-investigator of a contract funded by the U.S. National Institutes of Health to test flavivirus vaccines, including the U.S. National Institutes of Health dengue vaccine candidate, in clinical trials. This interest was assessed as personal, specific, and financially significant*.
- She has provided expertise to Vabiotech and the Instituto Butantuan in relation to the U.S. National Institutes of Health dengue vaccine, funded by the German Federal Ministry of Education and Research (BMBF) through a grant to the Dengue Vaccine Initiative. This interest was assessed as personal, specific, and financially significant*.

Wellington Sun (resigned from Working Group in February 2015)

- He is a co-inventor of one U.S. patent (#6638514) for WRAIR's live attenuated dengue vaccine, which is no longer being developed commercially, and co-inventor on another EU patent (#2462930) for the strategy of prime-boost in dengue vaccines. This interest was assessed as personal, specific, and financially insignificant*.

Stephen Thomas

- His institution, the U.S. Army, has cooperative agreements with Sanofi Pasteur, GSK, and Takeda guiding the co-development of dengue vaccine development activities, that may include in kind financial support for travel or other support provided to the US Army. This interest was assessed as non-personal, specific, and financially significant*.

Peter Smith

- He is a member of the Independent Data Monitoring Committee for Sanofi Pasteur’s dengue vaccine clinical trials. This interest was assessed as personal, specific, and financially significant*.

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* 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. EVIDENCE TO RECOMMENDATIONS TABLE AND GRADE TABLES

SAGE EVIDENCE TO RECOMMENDATIONS TABLE

More evidence that was made available to SAGE to support their recommendations on dengue vaccine can be found in this background paper of the Working Group.

Question: *Should the dengue vaccine be recommended, over no vaccination, to be administered to immunocompetent individuals (≥9years of age) in dengue-endemic countries to mitigate burden of severe dengue disease?*

Population: *Immunocompetent individuals (≥9years of age)*

Intervention: *Three doses of dengue vaccine in the context of routine dengue control interventions*

Comparison(s): *No vaccination in the context of routine dengue control interventions*

Outcome: *Hospitalized or severe dengue*

Background:

Dengue is a mosquito-borne virus with extensive distribution in the tropics and subtropics. Dengue is a high incidence disease, and hospitalized and severe dengue cause significant burden on health systems. The most common presentation of dengue is the sudden onset of fever accompanied by headache, pain behind the eyes, generalized myalgia and arthralgia, flushing of the face, anorexia, abdominal pain and nausea. Rash is frequently seen on the trunk. Criteria for severe dengue include any sign of severe plasma leakage leading to shock or fluid accumulation with respiratory distress, severe bleeding, or severe organ impairment. There is no specific anti-viral treatment for dengue. Due to advanced clinical case management, the case-fatality rate is <1%. At present, the only method to reduce the transmission of dengue virus is through vector control. There is a paucity of data showing an effect of vector control interventions on the incidence of human dengue cases.

The first dengue vaccine was licensed in December, 2015, and has now been licensed or submitted for licensure in several dengue-endemic countries. It is a three-dose vaccine administered 6 months apart and is indicated for use in individuals 9 years to either 45 years or 60 years, depending on the country.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	No ☐ Uncertain ☐ Yes ☒ Varies by setting ☐	Dengue is a major public health problem, with every WHO Region affected by dengue. In the last 60 years the incidence of clinical cases of dengue reported to WHO has increased 30-fold, with a much increased geographic range, including the expansion from predominantly urban to rural settings. Approximately 3.5 billion people live in dengue endemic countries. A recent prediction, based on available incidence and prevalence data and modelled globally, estimated 390 million dengue infections per year in 2010 (95% credible interval 284–528 million), of which about 25%, 96 million (67–136 million), manifest clinically (with any severity of disease)(Bhatt et al. 2013). WHO has estimated 500,000 hospitalizations for dengue annually, of which about 12,000 are fatal (SAGE Background Paper on Dengue Vaccines)	There have been efforts to develop dengue vaccines for decades, but it has proven to be one of the more difficult pathogens against which to develop a vaccine for a variety of reasons (SAGE Background Paper on Dengue Vaccines).
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	No ☐ Uncertain ☐ Yes ☐ Varies ☒	Vaccine efficacy over 25 months from the first dose among 9-16 year-olds, pooled from both CYD14 and CYD15 (post-hoc analysis), was 65.6% (95%CI 60.7-69.9). Protection was evident following the first dose and showed little variation up to one year following the third dose. VE against hospitalized dengue was 80.8% (95%CI 70.1-87.7) in participants first vaccinated > 9 years of	Vaccine efficacy in these first 25 months varied by infecting serotype (higher protection against DENV 3 and 4), age (higher protection in 9-16 year age group), and severity (higher protection against hospitalized and severe dengue). Most notably, vaccine efficacy was high among participants 9 years of age or older who were seropositive (i.e., had

			age. VE against severe dengue in the first 25 months of follow up in the two trials combined was 93.2% (95%CI 77.3-98.0) in participants >9 years of age. (SAGE Background Paper on Dengue Vaccines). Mathematical modelling suggests that in high transmission settings, the introduction of CYD-TDV in early adolescence through routine immunization could reduce dengue hospitalizations by 10-30% over the period of 30 years, representing a substantial public health benefit. The modelling predicted that the vaccine would be less beneficial in low transmission settings, due to the higher proportion of seronegative individuals, among whom the vaccine may have limited protective effect.	previous exposure to dengue) at baseline (81.9%, 95%CI 67.2-90.0), and lower among participants who were seronegative at baseline (52.5%, 95%CI 5.9-76.1). Serostatus and age were highly correlated in the population studied. There are no POC diagnostic tests that could be used to identify seropositives and seronegatives at the time of vaccination.
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐ *Uncertain* ☐ *Yes* ☐ *<u>Varies</u>* ☒	Data from Phase 2 and Phase 3 trials have not signaled any safety concern with regard to traditional safety considerations (reactogenicity, serious adverse events, etc.). CYD-TDV is well-tolerated. An increased risk of hospitalized and severe dengue was seen in the 2-5 year-olds in the Phase 3 trial in which this age group was included. This increased risk was large (relative risk 7.45 in Year 3), but diminished in Years 4 and 5. The Phase 2b trial in Thailand, CYD23/57, found similar effects in children under 6 years. The 2-5 year age group also has	There is a theoretical possibility that vaccination may be ineffective or may even increase that risk in those who are seronegative at the time of first vaccination. Because these subgroups cannot be identified, there cannot be separate recommendations for subgroups in an immunization program.

			the highest proportion of seronegatives. There are no data from the Phase 3 trials to suggest a similar increased risk in those aged 9 years or above, but most of these children were seropositive when first vaccinated.	
	Balance between benefits and harms	*Favours intervention* ☒ | *Favours comparison* ☐ *Favours both* ☐ *Favours neither* ☐ *Unclear* ☐	The benefits of the dengue vaccine have been measured in Phase 3 efficacy trials. The potential harms in the seronegative population aged 9 years and above are theoretical. From a population perspective, there is clear evidence of a positive impact of vaccination on severe and hospitalized dengue when the vaccine is used in a high transmission setting. For seronegative individuals, it is possible that the vaccine has no effect or theoretically could do harm, if their (lifetime) population risk of dengue was such that they would likely only receive one natural infection (which would then place them at a higher risk of severe or hospitalized dengue). However, the vaccine performance among seronegatives age 9 years and above requires further characterization to quantify risks and benefits. As serostatus cannot be easily determined at the time of vaccination, it is difficult to make individual-level decisions about vaccination based on serostatus in a population-based vaccination programme.	

	What is the overall quality of this evidence for the critical outcomes?	*No included studies* ☐ *Very low* ☐ *Low* ☒ *Moderate* ☐ *High* ☒ Effectiveness of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☒ *Moderate* ☒ *High* ☐ Safety of the intervention	GRADE high quality evidence for vaccine efficacy. Grade low quality of evidence for duration of protection beyond 2 years from first dose. Grade low quality of evidence for risk of severe/hospitalized dengue in seronegatives Grade moderate quality of evidence for risk of serious (non-dengue)adverse events following dengue vaccination	
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐ *Possibly important uncertainty or variability* ☒ *Probably no important uncertainty or variability* ☐ *No important uncertainty or variability* ☐ *No known undesirable outcomes* ☐	No data on public attitudes about desirable and undesirable outcomes.	Both demonstrated desirable and theoretical undesirable outcomes are based on risk of dengue. Thus, the outcomes are equally important. Whether some individuals are concerned about the theoretical risk in seronegatives to such an extent as to refuse vaccination is unknown.

	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ | Varies ☐	No evidence was retrieved on the values and preferences of the target population with respect to the demonstrated benefit in the trials and theoretical risks. In general, the target population is expected to be very supportive of a dengue vaccine.	In the context of implementation, it would need to be considered the most appropriate communication strategies for informed decision-making about vaccination.
RESOURCE USE	Are the resources required small?	No ☐ Uncertain ☒ Yes ☐ | Varies ☐	The price of the dengue vaccine has not yet been communicated. In terms of additional resources, the vaccine could be delivered through existing school-based immunization programs, if they are in place. Stress on the supply chain needs to be assessed. Additional contacts may be required, leading to a possible increase in operational costs to the health system.	Given the price of the vaccine and budget affordability, countries will need to consider whether the dengue vaccine is a priority intervention to fund.
	Cost-effectiveness	No ☐ Uncertain ☒ Yes ☐ | Varies ☐	Vaccination was predicted to be potentially cost-effective in settings with a seroprevalence at 9 years of age of 30-90%, if the vaccine can be purchased and delivered cheaply enough.	Countries should do cost-effectiveness assessments based on their own context, including country-specific hospitalization rates and costs.

EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *Reduced* ☐ Varies ☒	There has been no specific evaluation on how the dengue vaccine implementation may contribute to reducing health inequities. Dengue does primarily effect low and middle income countries, and reducing the disease burden would improve equity. Reducing the burden of catastrophic expenditures related to dengue disease in low-income families could reduce inequities within countries.	If the vaccine is not paid for by a government program, there is high risk that low-income families cannot afford vaccination, thus increasing health inequity.
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Countries should assess whether adequate resources can be allocated to implement and sustain dengue vaccination in the routine immunization schedule. This especially applies to low and middle income countries with limited resources, where dengue vaccination might be competing with other important public health interventions.	
	Which option is acceptable to target group?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Given the high burden of morbidity, it is presumed that the vaccination would be acceptable to the target group if the costs are covered by the health care provider.	

FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ | *Varies* ☐		The intervention is feasible, as has been demonstrated with vaccines administered in similar age groups.	If the vaccine is not paid for by a government program, there is high risk that low-income families cannot afford vaccination.	
Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings[7] ☒	
Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☒ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐	

[7] When considered at the population level and in settings meeting the criteria outlined in the recommendation

Recommendation (text)	Countries should consider introduction of CYD-TDV in geographic settings (national or subnational) with high dengue transmission, i.e. seroprevalence of approximately 70% or greater in the age group targeted for vaccination but not below 50%. Where possible, assessment of dengue transmission intensity should be supported by geographically relevant seroprevalence studies. Seroprevalence estimates should guide decision-making and introduction at subnational levels while noting that these are not precise indicators. Work is needed to identify routinely collected epidemiologic indicators that can be used to infer likely seroprevalence. Decisions about introduction require careful assessment at the country level, including consideration of local priorities, subnational dengue epidemiology, predicted impact and cost-effectiveness with country-specific hospitalization rates and costs, as well as affordability and budget impact. Vaccination should be considered as an integrated strategy together with well-executed and sustained vector control and the best evidence-based clinical care for all patients with dengue.
Implementation considerations	Due to the partial efficacy of the vaccine against dengue of any severity, careful communication is needed to inform vaccinees that they may still be at risk of dengue and of the importance of receiving all three doses and of adhering to other disease preventive measures.
Monitoring and evaluation	Monitoring of immunization coverage and disease surveillance, including risk of dengue over time in vaccinated individuals and duration of protection.
Research priorities	A number of research priorities specific to CYD-TDV and general to the dengue vaccine field are listed in section 11.7. The following were assessed as critical, to be addressed as soon as possible: • Risk of severe/hospitalized dengue over time in vaccinated seronegatives • Duration of protection / need for additional doses • Second-generation vaccines that include characteristics such as improved protection against all four dengue serotypes, single-dose, for use in younger age groups

GRADE TABLE 1

What is the efficacy of 3 doses of CYD-TDV in preventing clinical dengue in adolescents and adults 9-45 years of age in the first year following vaccination?

Population: 9-45 year-old adolescents and adults living in dengue endemic areas

Intervention: 3 doses of CYD-TDV administered 6 months apart

Comparison: Placebo

Outcome: Virologically-confirmed dengue occurring ≤ 12 months of completion of 3 doses

What is the efficacy of 3 doses of CYD-TDV in preventing clinical dengue in adolescents and adults 9-45 years of age in the first year following vaccination?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious[2]	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[3]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a high level of confidence that the true effect lies close to that of the estimate of effect on health outcome.**
	Conclusion			**CYD-TDV demonstrates statistically significant vaccine efficacy against virologically-confirmed dengue in the first 12 months following vaccination with three doses, although the degree of protection varies by age, infecting serotype, serostatus at baseline, and dengue severity.**

[1] CYD-TDV has been evaluated in two parallel Phase 3 clinical trials, known as CYD14 and CYD15. CYD14 was conducted in 5 countries in Asia (Indonesia, Malaysia, Philippines, Thailand, and Vietnam), with 5,234 participants aged 9-14 years at first vaccination (10,275 participants in the full trial population aged 2-14 years). CYD15 was conducted in 5 countries in Latin America (Brazil, Colombia, Honduras, Mexico, and Puerto Rico (US)), with 20,869 participants aged 9-16 years at first vaccination. In each of these trials, participants were randomized to vaccine and placebo in a 2:1 ratio. Because the

physical appearance of the vaccine and placebo was different, unmasked trial staff were responsible only for preparation and administration of injections and were not involved in the follow-up of trial participants. For the ascertainment of trial endpoints the trials were observer-masked. All serology testing was also performed in a blinded manner. In the per-protocol analysis (full trial populations monitoring from 1 month after the 3rd dose for 12 months), vaccine efficacy against dengue of any serotype was 56.5% (95%CI 43.8-66.4) in CYD14, and 60.8% (95%CI 52.0-68.0) in CYD15. In the 25 months following 1 doses of CYD-TDV (ITT analysis), vaccine efficacy against virologically-confirmed dengue pooled across the two studies was 59.2% (95%CI 52.3-65.0) and was consistent across studies. In both trials, vaccine efficacy was lower against serotypes 1 and 2 than against serotypes 3 and 4, was lower in individuals seronegative at baseline compared to seropositive at baseline, and was higher against more severe forms of dengue. Vaccine efficacy in those <9 years of age was lower than in those ≥9 years of age. While the endpoint led to variable vaccine efficacy estimates, the estimates were highly consistent for the same outcomes across trials. Vaccine efficacy was also measured in a Phase 2b study, CYD23/57, in 4,002 children aged 4 to 11 years in Ratchaburi Province, Thailand. The definition of fever, precipitating a diagnostic test for dengue, was slightly different to that used in the Phase 3 trials.

[2]Vaccine efficacy has been assessed only the 9-16 year population within the indicated age range of 9-45 or 9-60 years. Licensure has been granted based on immunological bridging, although there is no accepted correlate of protection. Although there is no correlate of protection to be used for extrapolation, it has been shown that serostatus at baseline is associated both with age and with higher titers post vaccination. Comparing PD3 titers from the vaccine efficacy studies to PD3 titers from immunogenicity studies in Vietnam (N=20 aged 18-45) and India (N=126 aged 18-45), titers in adults in endemic settings were typically statistically significantly higher than in the older children and adolescent trial population. Given efficacy was established in this younger population, it was extrapolated that efficacy would also be similar or better in comparable adult populations.

[3]A large effect is noted 59.2% (95%CI 52.3-65.0), although currently the score is not eligible for upgrade at the maximum score.

GRADE TABLE 2

What is the risk of hospitalized and severe dengue over time in adolescents and adults 9-45 years of age vaccinated with CYD-TDV who are seronegative at baseline?

Population: 9-45 year-old adolescents and adults with $PRNT_{50}$<10 against all four serotypes, living in dengue endemic areas

Intervention: 3 doses of CYD-TDV administered 6 months apart

Comparison: Placebo

Outcome: Hospitalized or severe dengue occurring > 12 months after completion of the first three doses

What is the risk of hospitalized and severe dengue over time in adolescents and adults 9-45 years of age vaccinated with CYD-TDV who are seronegative at baseline?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		3 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	None serious[2]	0
		Inconsistency	None serious	0
		Indirectness	Serious[3]	-1
		Imprecision	Serious[4]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[5]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a low level of confidence that the true effect lies close to that of the estimate of effect on health outcome.**
	Conclusion			**There are insufficient data to inform whether seronegative individuals 9 years of age or older who are vaccinated may be at some point in time at higher risk of severe or hospitalized dengue than those do not receive vaccine.**

[1]CYD-TDV has been evaluated in two parallel Phase 3 clinical trials, known as CYD14 and CYD15. CYD14 was conducted in 5 countries in Asia (Indonesia, Malaysia, Philippines, Thailand, and Vietnam), with 5,234 participants aged 9-14 years at first vaccination (10,275 participants in the full trial population aged 2-14 years). CYD15 was conducted in 5 countries in Latin America (Brazil, Colombia, Honduras, Mexico, and Puerto Rico (US)), with 20,869 participants aged 9-16 years at first vaccination. In each of these trials, participants were randomized to vaccine and placebo in a 2:1 ratio. Because the physical appearance of the vaccine and placebo was different, unmasked trial staff were responsible only for preparation and administration of injections and were not involved in the follow-up of trial participants. Risk of hospitalized and severe

dengue was also assessed in the Phase 2b trial in Thailand (CYD23/57). For the ascertainment of trial endpoints the trials were observer-masked. All serology testing was also performed in a blinded manner. After 2 years of active phase of follow up, participants were followed for hospitalized and severe dengue using an enhanced passive surveillance system. Only a subset of trial participants were included in the immunogenicity subset, for which baseline serostatus was known. During the course of the hospital-based surveillance, a signal emerged from the youngest age group (2-5 years, an age group only included in CYD14). During both Years 1 and 2 of active follow-up, the RR of hospitalized dengue in the 2-5 year age group was 0.6. During Year 3, there were 15 hospitalized cases in the CYD group compared to 1 hospitalized case in the placebo group (2:1 randomization), a RR of 7.45 (95%CI 1.15-313.80). During Year 4 and Year 5, the cumulative relative risk for Year 3 onwards diminished to 1.424 (95%CI 0.58-3.99) and 1.495 (95%CI 0.27-15.15), respectively. The cumulative relative risk during the entire trial period to date is 1.256 (95%CI 0.76-2.13). In contrast, across older age groups (6-8, 9-11, and 12-16 years), an elevated risk was not seen consistently across the trials.

[2]Only a subset (2,000 participants) from each trial were included in the immunogenicity subset, but this was downgraded under “Imprecision” as the confident intervals are very wide.

[3]Given the small numbers of participants in the immunogenicity subset and thus the numbers of cases that occur in this small population is insufficient to characterize well the risk in seropositive individuals. In CYD14 the immunogenicity subset was 1983 children and in CYD15 the immunogenicity subset was 1944 children, across all ages in the trials and CYD and placebo groups. Among trial participants 9 years of age or older, seropositivity was approximately 80%, thus there were few hospitalized dengue cases that occurred among seronegatives 9 years of age or older who were also included in the immunogenicity subset. Some inference may be drawn from the 2-5 year trial population in CYD14, which had a higher proportion of seronegatives. However, this is downgraded for indirectness.

[4]The confidence intervals for effect is very wide due to the small numbers in the immunogenicity subset, and so this is downgraded for imprecision.

[5]A large effect is noted in the 2-5 year age group (RR hospitalized dengue in Year 3 7.45(95%CI 1.15-313.80)), however as it is an indirect measure of serostatus, the score was not upgraded.

GRADE TABLE 3

What is the risk of other serious adverse events (non-dengue) in adolescents and adults 9-45 years of age vaccinated with CYD-TDV?

Population: 9-45 year-old adolescents and adults living in dengue endemic areas

Intervention: 3 doses of CYD-TDV administered 6 months apart

Comparison: Placebo

Outcome: Serious adverse events (non-dengue)

What is the risk of other serious adverse events (non-dengue) in in adolescents and adults 9-45 years of age vaccinated with CYD-TDV?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		13 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	Serious[2]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of effect on health outcome.**
	Conclusion			**There is no evidence of an association between CYD-TDV and non-dengue serious adverse events based on clinical trials.**

[1]Safety data have been generated in the course of multiple Phase 1, 2, and 3 trials (13 Contributing studies to the 9-60y pool are: CYD12, 13, 22, 24, 28, 30, 47, 23, 17, 32, 14, 15, 51). In the Phase 3 trials, the number of serious adverse events (SAEs) was similar between CYD and placebo group. Related SAEs up to 28 days after a CYD injection occurred in 6 subjects (headache and polymyalgia rheumatic in adults, and allergic urticaria, asthma, acute polyneuropathy, and tension headache in 9-17 year-old participants). An additional SAE was classified as related by the investigator in the 28 days to 6 months post CYD injection (blighted ovum), and 1 SAE of convulsion was judged to be related by the sponsor (not the Investigator). No immediate anaphylactic shock has been reported post-vaccination.

[2]There are a limited number of trial participants beyond 16 years of age to assess the risk of serious adverse events in the 17-45 year population. Even for the 9-16 year-olds, a population including in the Phase 3 trials, risks of rare serious adverse events would require further assessment in post-licensure studies.

GRADE TABLE 4

What is the duration of protection in adolescents and adults 9-45 years of age vaccinated with CYD-TDV?

Population: 9-45 year-old adolescents and adults living in dengue endemic areas

Intervention: 3 doses of CYD-TDV administered 6 months apart

Comparison: Placebo

Outcome: Virologically-confirmed dengue occurring > 12 months of completion of 3 doses

What is the risk of other serious adverse events (non-dengue) in in adolescents and adults 9-45 years of age vaccinated with CYD-TDV?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	Very serious[2]	-2
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a low level of confidence that the true effect lies close to that of the estimate of effect on health outcome.**
	Conclusion			**There is insufficient data from the Phase 3 trials to assess waning immunity against VCD. Further assessment is required.**

[1]CYD-TDV has been evaluated in two parallel Phase 3 clinical trials, known as CYD14 and CYD15. CYD14 was conducted in 5 countries in Asia (Indonesia, Malaysia, Philippines, Thailand, and Vietnam), with 5,234 participants aged 9-14 years at first vaccination (10,275 participants in the full trial population aged 2-14 years). CYD15 was conducted in 5 countries in Latin America (Brazil, Colombia, Honduras, Mexico, and Puerto Rico (US)), with 20,869 participants aged 9-16 years at first vaccination. In each of these trials, participants were randomized to vaccine and placebo in a 2:1 ratio. Because the physical appearance of the vaccine and placebo was different, unmasked trial staff were responsible only for preparation and administration of injections and were not involved in the follow-up of trial participants. For the ascertainment of trial endpoints the trials were observer-masked.

[2]The study design of CYD14 and CYD15 included 25 months of active surveillance followed by hospital-based surveillance. Thus, duration of protection against VCD cannot be assessed. However, active surveillance is currently being reinstated. Data on hospitalized dengue has been collected throughout the trial period, though with different surveillance systems in the Active and Hospital Phases. With the limitations of this change in surveillance and that the CYD and placebo groups

have different histories of dengue exposure at the start of later time intervals, it is one source of data available now to assess protection over the period of the trial.

For hospitalized dengue in ages included in the indication (9-16 years), the point estimate of relative risk of hospitalized dengue remains below 1, suggesting a sustained protective effect. The point estimates year-by-year are variable, although in many instances the point estimate becomes closer to one as time progresses. In all age groups, the relative risk of severe dengue among vaccinated compared to controls is lower during the active phase than during the hospital phase. These data may suggest potential (though unconfirmed) waning protection across all age groups.

Comparative modelling of dengue vaccine public health impact (CMDVI)

17/03/2016

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1. Executive Summary

A summary of the key results from the modelling comparison may be found in the Background Paper on Dengue Vaccines, Section 8.

2. Background

Recent estimates indicate that Dengue virus (DENV) causes 50 [1] to 96 [2] million cases per year of symptomatic disease. While DENV is prevalent across the tropics and subtropics, transmission intensity is highly variable spatially and temporally. There are four antigenically distinct DENV serotypes (DENV1-4) which co-circulate in most dengue endemic-areas. These serotypes cross-react immunologically but cross-protection is imperfect, meaning an individual can have multiple infections during their life. The first (primary) DENV infection typically causes no or mild disease and is thought to induce life-long homologous immunity as well as a transient period of heterologous protection [3,4]. Someone experiencing his second DENV infection has a substantially increased risk for severe illness, hypothesised to result from antibody dependent enhancement (ADE), whereas subsequent infections are mostly associated with milder symptoms [5].

A highly efficacious vaccine that provides long-lived protection against all four DENV serotypes would be the optimal tool to substantially reduce the burden of DENV [6]. After 20 years of development [7], Sanofi Pasteur has recently demonstrated the safety and efficacy of Dengvaxia®, a recombinant, live, attenuated, tetravalent dengue vaccine, administered in 3 doses at 6 months intervals, in large phase III clinical trials in Latin America and South-East Asia [8,9]. Overall efficacy of 60.3% (95% CI, 55.7 to 64.5) was shown against virologically confirmed clinical dengue in children between 2 and 16 years during the 25-month active surveillance phase. Efficacy varied by age, serotype and country and was about twice as high in children who were seropositive when vaccinated as in those who were seronegative.

Following the active surveillance phase of the trials, passive detection of virological confirmed hospitalised cases has been continued during the long-term follow-up period of 4 years. The results from the first year of long-term follow-up showed that the vaccine remained protective in all age-

groups except among 2-5 year old children where vaccinees had a higher incidence of hospitalisation with virologically confirmed DENV than unvaccinated controls [10]. However, among all age groups the relative risk for hospitalisation for virologically confirmed dengue of vaccinated versus unvaccinated individuals was higher than the relative risks seen in the active phase (*i.e.* efficacy was reduced).

By February 2016, Mexico, Philippines, Brazil and El Salvador were the first four countries to approve Dengvaxia® for individuals aged 9 to 45 living in endemic areas. The vaccine has been submitted for approval in over 10 other endemic countries. However, there are as yet no data from post-licensure use of the vaccine.

3. Inclusion criteria for models

In April 2015 the World Health Organisation (WHO) initiated an open call for modellers to participate in a consortium called "Comparative modelling of dengue vaccine public health impact" (CMDVI) [11]. The purpose of the consortium was to generate model based predictions of the long-term safety, health and economic impact of Dengvaxia® to inform recommendations from the Strategic Advisory Group of Experts (SAGE) on Immunization. Any group was invited to join that had a transmission dynamic model of dengue vaccination which had been used to examine the potential public health impact of prophylactic vaccination and where results and key features have been documented in either a peer reviewed journal article, or an unpublished technical documentation to the standard of a journal article. Of the 10 groups that originally applied and complied with these inclusion criteria two groups withdrew subsequently due to time constraints. The remaining groups were from Duke University, Exeter University / Oxford University, Johns Hopkins University / University of Florida, Imperial College, University of Notre Dame, Sanofi Pasteur, University of Florida, and University of Western Australia. The process by which the models were chosen as well as the final modelling group selection was reviewed and approved by WHO's Immunization and Vaccines-related Implementation Research Advisory Committee (IVIR-AC) in June 2015.

Because of the complexity of the model in combination with time constraints the UWA model has not yet been compared with trial outcomes. Hence the model was excluded from the main report. Preliminary results are included in an appendix.

4. Comparison of model assumptions

The models used in the exercise are described in detail elsewhere [12–18]. In brief, all models tracked infections due to all four serotypes, included cross-immunity or cross-protection between serotypes (except of the Exeter/Oxford model) and explicitly included vector dynamics (except of the Duke University model). Table 1 summarises the main differences between the models. Half the models were deterministic compartmental models, while the other half were stochastic simulation models (also called agent-based models). The former have the advantage of being able to model larger populations, being more easily generalizable and faster to run, while the latter allow more flexibility about individual characteristics and spatial aspects to be included. Four models were formally fitted to the active and hospital phase Dengvaxia® trial data (all of them deterministic). In contrast to the other models which had been fitted to the publically available aggregated data, the Sanofi model was fitted to unpublished disaggregated data from the active phase of the trials [16], and hence incorporated differences in outcomes according to serotypes as well as country specificities regarding transmission intensity and hospitalisation rates. In the version used for the CMDVI exercise, vaccine waning rates and country attack rates for year 3 were further adapted to the results of the first year of long-term follow-up. Models which were not fitted to the data made

use of vaccine parameter estimates provided by the models that were fit to the data (see Appendix Table 1). In addition to varying in epidemiological and immunological assumptions, models varied in terms of the types of uncertainty which were included in the model runs and therefore the interpretation of the uncertainty bounds around model outputs. All models used demographic parameters typical of dengue-endemic middle-income countries.

Table 1: Comparison of models contributing to exercise and overview of main differences

Group	Model type	Model fitted to trial data	Uncertainties represented in model output	Increased infectiousness for symptomatic infections	Demography assumed
Sanofi Pasteur	Deterministic non-spatial	Yes	Parametric & timing of vaccine introduction	Yes	Brazil-like
Hopkins/UF	Deterministic non-spatial	Yes	Timing of vaccine introduction	Yes	Brazil-like
Imperial	Deterministic non-spatial	Yes	Parametric & timing of vaccine introduction	Yes	Brazil-like
Duke	Deterministic non-spatial	Yes	Parametric	No	Brazil-like
UF	Stochastic spatial	No	Parametric & stochastic variation	Yes	Mexico
UWA	Stochastic spatial	No	Parametric & stochastic variation	No	Thailand
Notre Dame	Stochastic spatial	No	Parametric & stochastic variation	Yes	Peru
Exeter/Oxford	Stochastic spatial	No	Stochastic variation	No	Generic (65 y mean lifespan)

5. Mode of vaccine action and vaccination policies examined

A model of vaccine action and a set of vaccination policies of interest were agreed upon with the SAGE working group on dengue [19]. The mode of action was a parsimonious one capable of reproducing the active phase and long-term follow-up results seen in the phase III trials (Figure 1). It consists of three components:

1. Impact of vaccine acquired immunity on the risk of infection: the rapid change from a high level of protection against hospitalised disease seen in the active phase of the trial to a lower level of protection (or increase in risk in 2-5 year olds) seen in the long-term follow-up data implies vaccine-induced protection decays rapidly. A parsimonious explanation for this observation is that vaccination acts similarly to natural infection in providing short-lived heterologous protection against infection. All models used in this exercise assumed that vaccination generates short-lived protection in seronegative individuals; two models (Notre Dame and Exeter/Oxford) additionally assumed such protection occurs in seropositive recipients while another model (Duke) assumed such protection was against disease rather than infection.
2. Impact of vaccine acquired immunity on risk of disease given infection: vaccination acts like a natural silent infection and moves individuals along the 'infection line' (see Figure 1).

Following vaccination, breakthrough infections in individuals with no pre-existing immunity before vaccination behave as natural secondary infections (here, referred to as primary breakthrough infections). Breakthrough infections in individuals who were vaccinated after experiencing one natural infection behave like natural tertiary infections (here, secondary breakthrough infections), and tertiary breakthrough infections like quaternary. Under this model, once short-lived heterologous protection decays in individuals who were vaccinated when seronegative, for their next infection they are at higher risk of dengue disease (particularly severe disease) than they would have been prior to vaccination; although, for subsequent infections they are at decreased risk. Conversely, vaccination confers long-lived high level protection against disease in individuals who are vaccinated after a single infection, since their first breakthrough infection after vaccination will have the much lower risk of disease associated with natural tertiary infection.

3. Effect of breakthrough infections on immune status of vaccinated individuals: under the above assumption that vaccination acts akin to a silent natural infection, all models assumed that a primary (breakthrough) infection in a vaccinated individual is equivalent, in terms of the immunity that it generates, to vaccination of an individual who has undergone a primary infection.

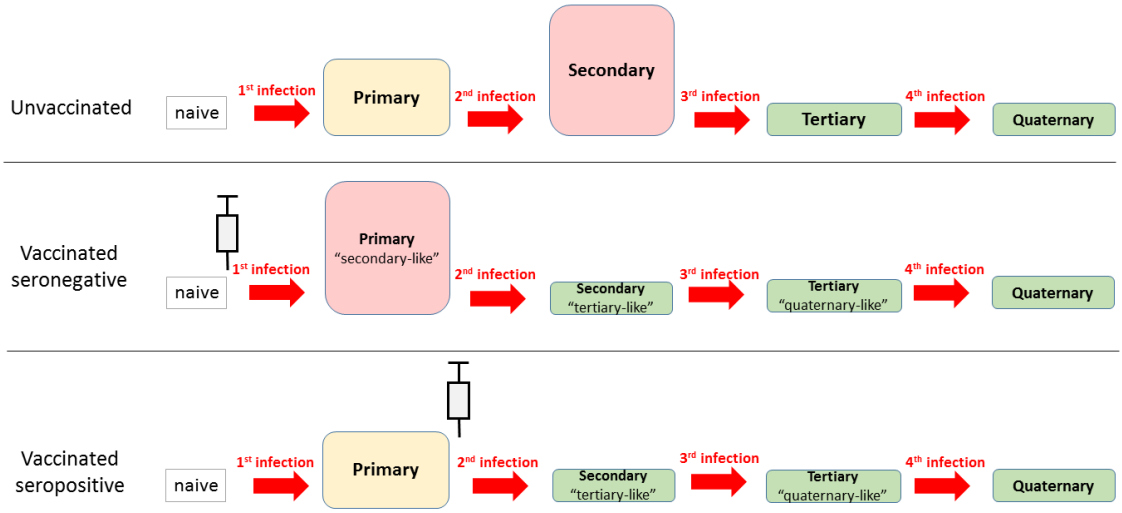

Figure 1: Assumed vaccine mode of action. The syringe symbol indicates timing of vaccination and red arrows indicate exposure to dengue infection. The height of the boxes illustrate the probability of severe symptoms occuring. Four potential infections are shown, but the number typically experienced by an individual over their lifetime is determined by the transmission intensity of dengue in a setting, ranging from 1 or fewer in very low transmission settings (SP9=10% or 30%) to 4 in the highest transmission settings (SP9=90%).

The default policy considered was routine vaccination of 9-year old children in a 3-dose schedule where doses are administered 6 months apart. For simplicity and because single dose efficacy is uncertain, perfect completion of the 3-dose schedule following receipt of the initial dose was assumed with a coverage level of 80%. Alternative strategies examined 50% coverage, addition of a

3-dose catch-up campaign of 10-17 year olds at 80% vaccine coverage and alternative ages of vaccine administration between 10 and 18 years.

The outcomes examined were the impact of vaccination on infections, symptomatic dengue, hospitalised dengue and deaths over a 10 and 30 year period post vaccine introduction. Case definitions for symptomatic dengue and hospitalised dengue were chosen in accordance to the phase III trials (which employed intensive active case finding) so model predictions of incidence cannot be directly compared with routine surveillance data which typically relies on much less sensitive passive detection but rather represent the full burden of dengue disease regardless of health care attendance.

The phase III trials were not powered to look at vaccination impact on death. We therefore assumed that efficacy against death was the same as that against hospitalised dengue disease, and each models assumed a probability of death in the range of 0.05% to 0.09% for symptomatic dengue cases (Appendix Table 1), based on a review of surveillance data and published studies [1,20–23]. Deaths were assumed to occur in a fixed proportion of symptomatic and/or hospitalised cases, and hence are omitted from the description of the epidemiological impact of vaccination although included in the economic evaluation.

As the trial results show different effects of vaccination depending on the serostatus of the recipient, all results were generated for a range of different dengue transmission intensities. Transmission intensity was characterised as the average proportion of 9 year olds who are seropositive prior to vaccine introduction (labelled SP9) and ranged between 10% (very low transmission) and 90% (very high transmission intensity). For comparison, the baseline seropositivity rate in children 9 to 16 years old in the trial settings in Latin America was between 53% in Mexico and 92% in Colombia [9]. Settings with 10% SP9 are unlikely to be endemic but rather frequently exposed due to proximity to endemic areas.

6. Health economic evaluation

Methodological framework

Health effects were measured in terms of disability adjusted life years (DALYs). In the base case, a public health care payer perspective was used with costs inflated to 2014 USD. A time horizon of 30 years was used consistent with the epidemiological modelling, but benefits from averted mortality are accrued over the entire lifetime of the individual. Costs and health effects were discounted at 3% per year. Sensitivity analyses were conducted using a societal perspective (using the friction cost approach [24]) and no discounting for health effects.

Because both vaccine procurement and delivery costs are unknown, outcomes are presented in terms of the threshold cost per vaccinated person, *i.e.* the maximum amount that could be paid (for procurement and delivery of three doses) to fully vaccinate someone before vaccination stops being cost-effective. This is defined as the sum of the incremental cost savings due to vaccination (to the health care provider or society) and incremental DALYs averted due to vaccination, with the latter monetised by multiplying with the threshold cost per DALY averted.

Threshold cost per DALY

The threshold cost per DALY averted is the incremental cost to the health service or to society of saving an extra year of disability-free life. The use of ad hoc GDP per capita based thresholds for decision making has been criticised [25,26] and is now strongly discouraged by WHO. Instead, we take the approach of comparing the incremental cost effectiveness rations (ICERs) of other

interventions that might be displaced by investment in dengue vaccination (see Table 1), i.e. the cost of each DALY averted through these other interventions. The ICERs for rotavirus, pneumococcal and human papillomavirus vaccination in comparable settings have been estimated to be in the range of $200 - $2,000 [27–29]. Case management of dengue has been estimated to have an ICER of around $200, while chemical and environmental vector control may have an ICER around $2,000 - $14,000 depending on the setting [30] (Appendix Table 2).

However, most international health economic evaluations have used a discount rate of 3% a year for both costs and health effects in their base case. Hence for our sensitivity analysis where health effects are not discounted, the ICERs of these interventions (and hence the threshold cost per DALY averted) would decrease. To estimate the reduction, we calculated the ratio between the ICER of different vaccines in low and middle income country settings when health effects are discounted at 3% and 0% (in both cases, costs were discounted at the same rate as health effects because there are few vaccine studies that examine differential discounting). The ratio ranged from 0.22 (HPV vaccination in Brazil [27]) to 0.40 (rotavirus vaccination in Vietnam [31]) to 0.46 (pneumococcal conjugate vaccination in Kenya [32]).

Hence for analyses in which we discount both costs and health benefits, we set a base case threshold cost per DALY of $2,000 but vary this up to $10,000, but then multiplied these values by 0.4 (giving costs per DALY of $800-$4000) when using a discount rate of 0% for health effects.

Economic parameters.

Costs and DALYs incurred as a result of dengue were estimated from the literature (see Table 2). Costs of dengue treatment were estimated using Brazil as a representative of an upper middle income Latin American country. As a sensitivity analysis unit costs estimated in the Philippines are used, representing a lower middle income South-East Asian country. The use of these parameters does not imply that the results represent the cost-effectiveness of dengue vaccination in Brazil or the Philippines, which would require a single-country economic evaluation using local epidemiological data.

Table 2: Overview of assumed DALYs and costs used in health-economic analysis, together with references that were used to estimate (through rounding) these values

	Brazil-like setting	Philippines-like setting
DALYs incurred		
Symptomatic dengue	0.006 [33]	0.006 [33]
Severe dengue	0.02 [33]	0.02 [33]
Costs from public payer perspective		
Symptomatic case	60 [34]	20 [10,35]
Hospitalised case	200 [9,34]	400 [8,35]
Costs from societal perspective		
Symptomatic case	200 [8,9]	40 [8,9]
Hospitalised case	500 [8,9]	500 [8,9]
Fatal case	11000	3000

7. Results

Comparison of model fits to trial data

Model results were compared to country-aggregated results from the South-East Asian trial (CYD14; Figure 2). In particular, comparisons were made to (i) age-stratified seropositivity at time of vaccine receipt, (ii/iii) age/serostatus-stratified attack rate for virological confirmed dengue in both the vaccine and the control arms during the active phase, and (iv) age stratified hospitalisation rate for dengue in both the vaccine and the control arms during the first year of the long term follow-up. We here compare model results against trial data that was aggregated over all phase III sites; no models (other than the Sanofi one) attempt to reproduce the variation in trial results seen between sites. All models matched the aggregate data well, with model estimates generally overlapping the observed data. One noticeable difference between models relates to hospitalisation rates in the 2-5 year-old age group during long-term follow-up, with two models (Sanofi and UF) not capturing the increased risk observed in vaccinated participants and slightly overestimating efficacy in the 6-11y age group. Conversely, most models that capture the excess risk in 2-5 year-olds in the long term follow up underestimate vaccine efficacy for the 12-14y age group.

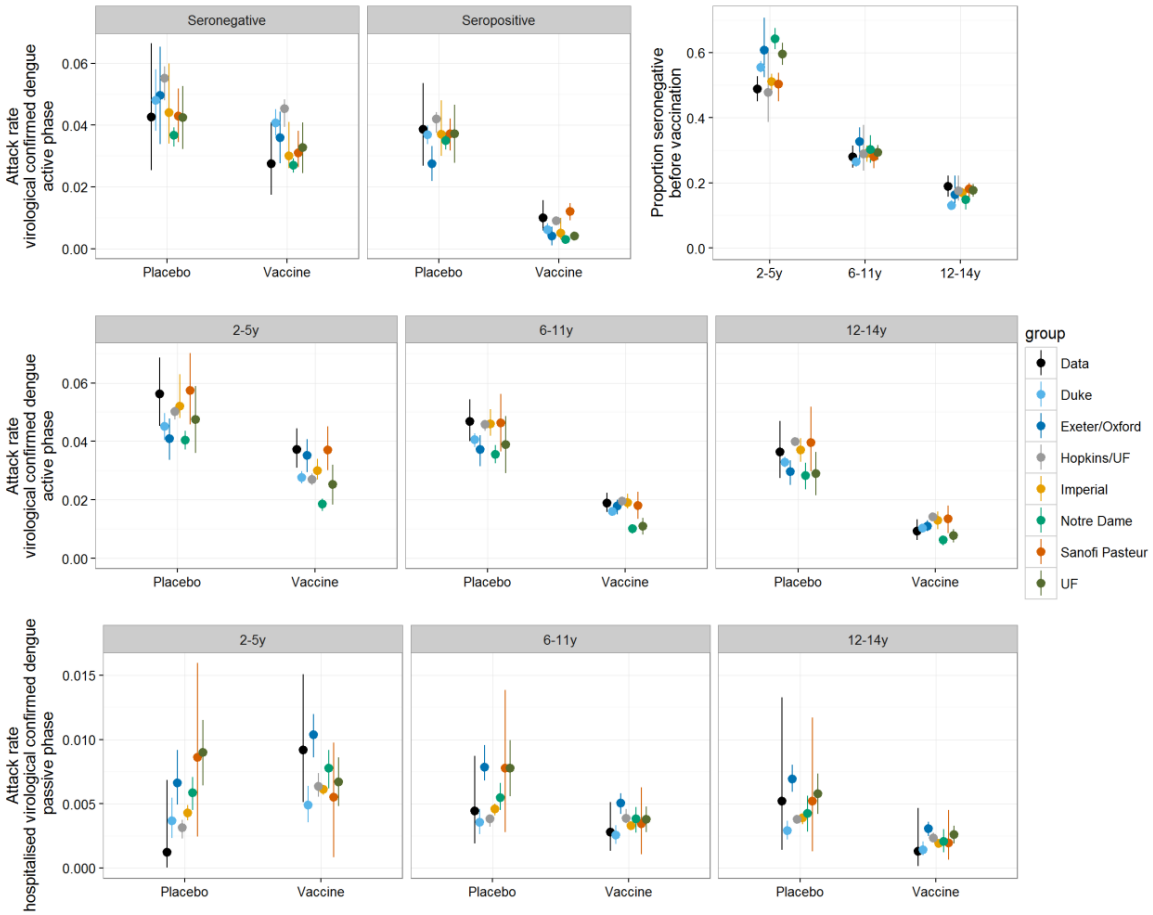

Figure 2: Comparison of aggregated CYD14 phase III and long term follow up trial results with model predictions. Dots report mean estimates and error bar the 95% range of simulations.

Transmission dynamics in the absence of vaccination

In the absence of vaccination, all models exhibit similar dynamics in terms of age-incidence distributions (Figure 3) and predicted seroprevalence by age (Figure 4). In settings with very low transmission intensity (SP9 = 10%), the burden of DENV disease is fairly evenly distributed among age groups in the absence of vaccination. As transmission intensity increases, disease burden shifts towards childhood with 35 to 70% of all dengue hospitalisations occurring in children younger than 9 years (Figure 3). Note, that due to time constraints (and preliminary inconsistencies) the results for the Exeter/Oxford model for the SP9=10% and SP30% were excluded from this report.

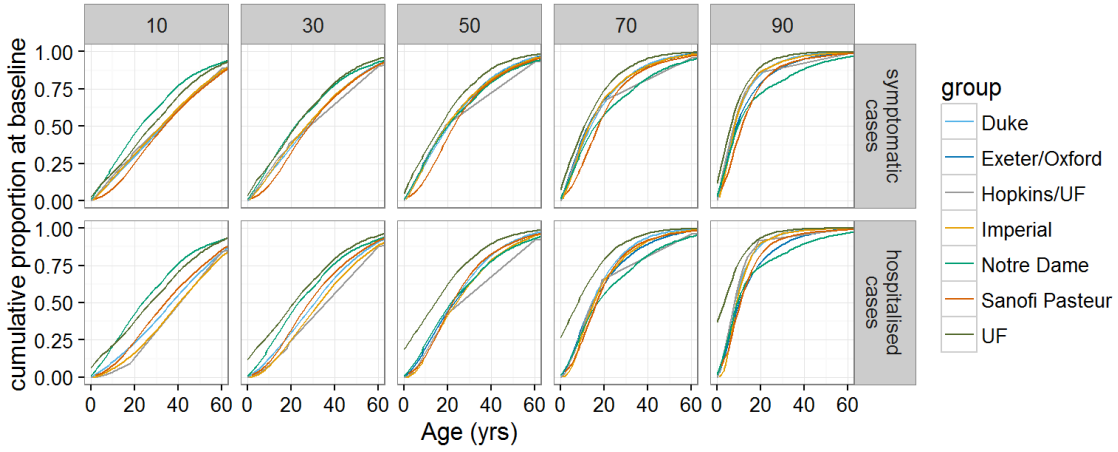

Figure 3: The cumulative age distribution of symptomatic cases and hospitalised cases before the start of vaccination

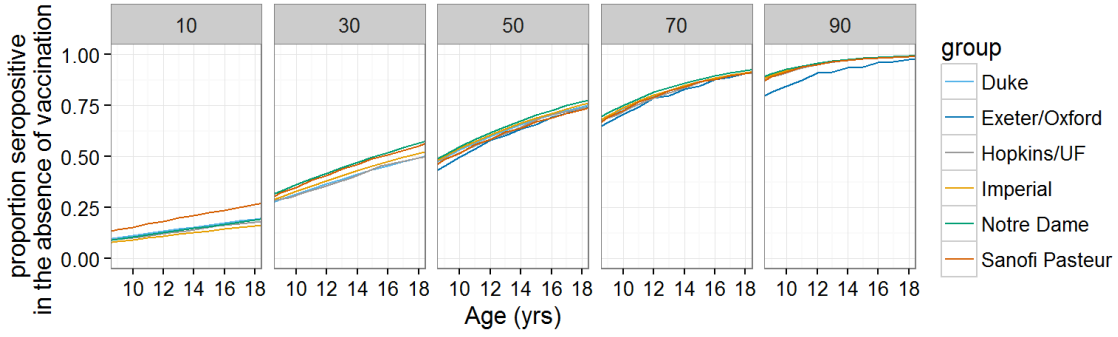

Figure 4: The age-stratified proportion of seropositive individuals before the start of vaccination

Population impact of routine vaccination of 9 year-olds

In high transmission settings with SP9 ≥ 70% , all models consistently predicted that introduction of vaccination of 80% of 9 year olds would lead to a 10-30% reduction in symptomatic and hospitalised dengue cases over the first 30 years of the policy (Figure 5 & Table 3). Similarly, in settings with very low transmission intensity all but one model predicted an increase in DENV hospitalisations following vaccine introduction.

In settings with SP9 between 30-50% predictions were more variable between models. At SP9=30% models differed in whether the impact of vaccination on hospitalised DENV cases was predicted to be detrimental or beneficial. Models which better reproduced the risk increase in 2-5 year olds in

the long-term follow-up tended to predict that vaccination at age 9 would increase hospitalisations in this setting, while other models predicted a beneficial effect of vaccination. At SP9=50% all models predicted a decrease in hospitalisation risk following vaccination.

In settings with SP9≥50% the impact of DENV vaccination was predicted to accrue almost linearly over time (Figure 6). This reflects most models predicting that the main impact from vaccination is due to direct effects – a result of the assumption that vaccination leads to only a transient period of protection against productive infection. However, any increase in either symptomatic cases or hospitalisations following vaccination in the SP9≤30% settings is consistently predicted only to become visible after a honeymoon period of about 10 years.

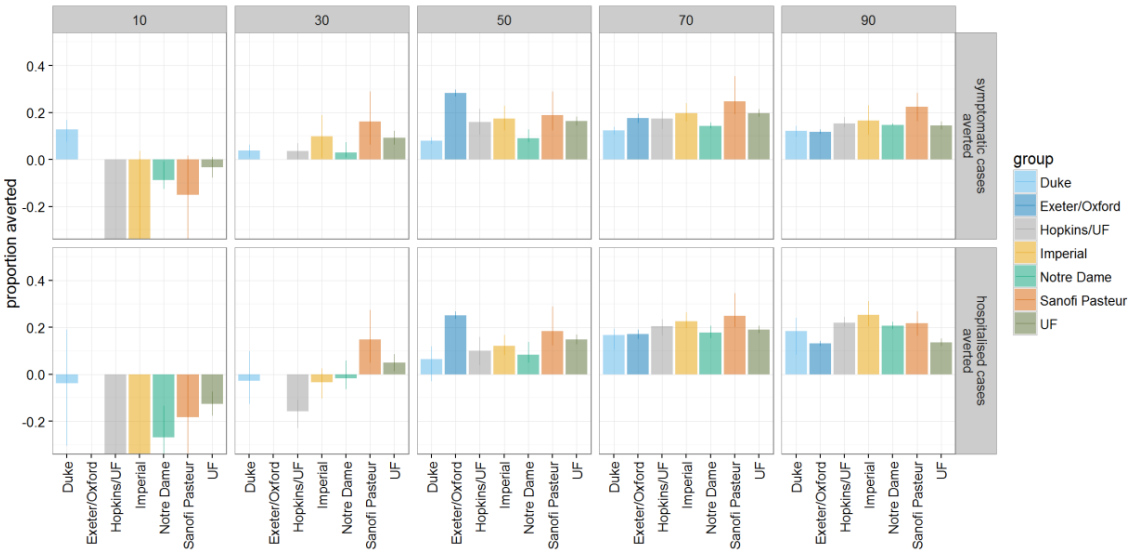

Figure 5: The proportion of symptomatic and hospitalised DENV cases averted within 30 years after vaccine introduction in the reference scenario. The bars represent the mean and the error bars the 95% range over multiple simulations.

Table 3: The proportion of hospitalised DENV cases averted within 30 years after vaccine introduction in the reference scenario. Mean and 95% range over multiple simulations are presented.

	SP9=10%	SP9=30%	SP9=50%	SP9=70%	SP9=90%
Duke	-0.04 (-0.3-0.19)	-0.03 (-0.13-0.1)	0.07 (-0.03-0.12)	0.17 (0.1-0.2)	0.18 (0.08-0.24)
Exeter/Oxford	-	-	0.25 (0.24-0.27)	0.17 (0.15-0.19)	0.13 (0.12-0.14)
Hopkins/UF	-2.4 (-2.47--2.35)	-0.16 (-0.23--0.11)	0.1 (0.04-0.16)	0.2 (0.16-0.23)	0.22 (0.2-0.24)
Imperial	-1.33 (-1.9--0.63)	-0.03 (-0.1-0.02)	0.12 (0.08-0.17)	0.23 (0.2-0.26)	0.25 (0.21-0.31)
Notre Dame	-0.27 (-0.36--0.13)	-0.02 (-0.06-0.06)	0.08 (0.05-0.14)	0.18 (0.15-0.21)	0.21 (0.19-0.22)
Sanofi Pasteur	-0.18 (-0.44-0)	0.15 (0.05-0.27)	0.18 (0.12-0.29)	0.25 (0.2-0.34)	0.22 (0.17-0.27)
UF	-0.13 (-0.18--0.07)	0.05 (0.01-0.08)	0.15 (0.13-0.17)	0.19 (0.17-0.21)	0.14 (0.12-0.15)

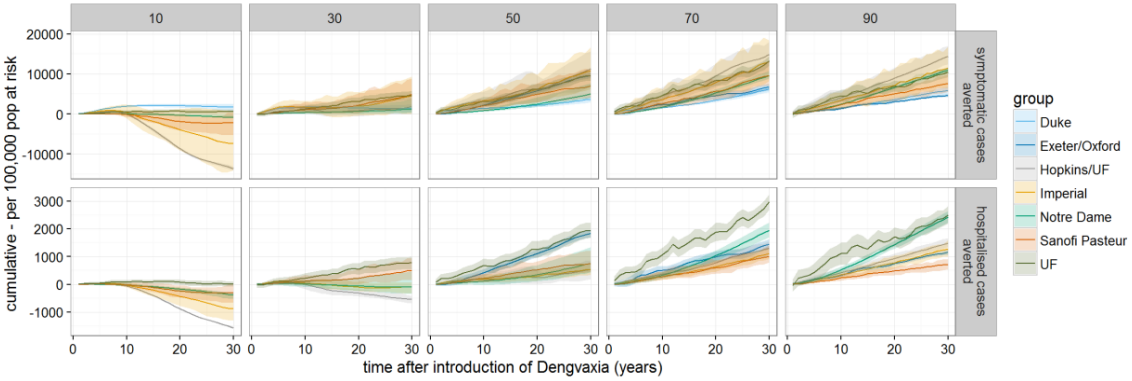

Figure 6: Predicted cumulative number of symptomatic and hospitalised DENV cases averted per 100,000 population over the 30 years after the start of routine vaccination (reference scenario). Lines represent the mean and the shaded region of the respective colour the 95% range over multiple simulations.

Individual-level impact of routine vaccination of 9 year-olds

As phase III trial results may imply differential vaccine efficacy by serostatus at the time of vaccination we also derived the impact of vaccination on an individual rather than population level. For such the first vaccinated cohort was followed over 30 years post vaccination. In every transmission setting, vaccination substantially reduced the risk of symptomatic or hospitalised disease in recipents who were seropositive at the time of vaccination. Conversely, in settings with low dengue endemicity (SP9≤30) recipients seronegative at the time of vaccination were predicted to be at increased risk for hospitalisation over a 30 year period in some models (Figure 7). This increased risk persisted into settings with moderate endemicity for some models.

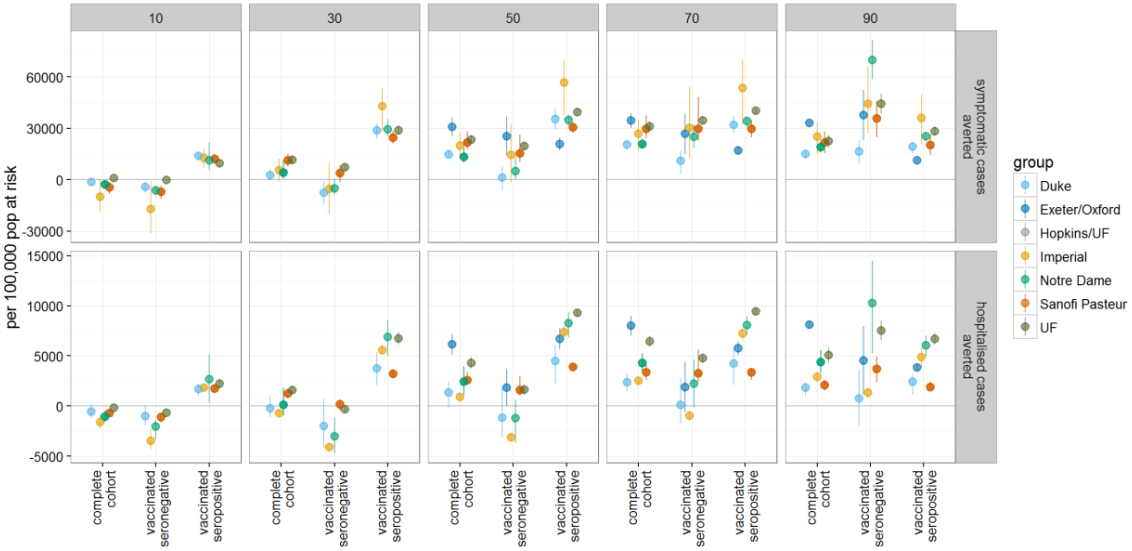

Figure 7: The number of symptomatic and hospitalised DENV cases averted per 100,000 population in the first vaccinated cohort within 30 years after vaccination. The effects of vaccination are stratified into the effects in the complete first cohort, those individuals who were seropositive at time of vaccination and those who were seronegative at time of vaccination.

Effect of varying vaccination coverage

Reducing vaccine uptake from 80% to 50% reduced the impact of vaccination proportionately, both for instances where the vaccine is predicted to be beneficial and where it is predicted to increase the risk for symptomatic dengue or hospitalisation. Since the majority of the predicted impact is gained from direct vaccine effects, impact scaled almost linearly with coverage for all models, meaning the proportion of cases averted per vaccine dose given is similar for 50% and 80% uptake (Figure 8).

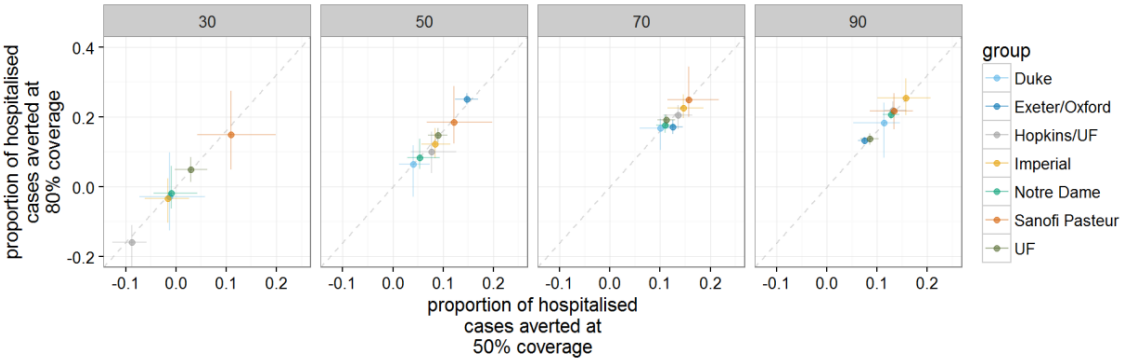

Figure 8: The proportion of hospitalised DENV cases averted in the 30 years after vaccine introduction comparing vaccine coverage of 80% with vaccine coverage of 50%. The grey, dashed line represents those instances where both strategies prevent the same number of cases per dose of vaccine assuming that after 10 years the latter strategy has used 5/8 times less doses. SP9=10% scenario not shown for clarity (most models predicted an increase in long-term population risk of DENV hospitalisations for this scenario).

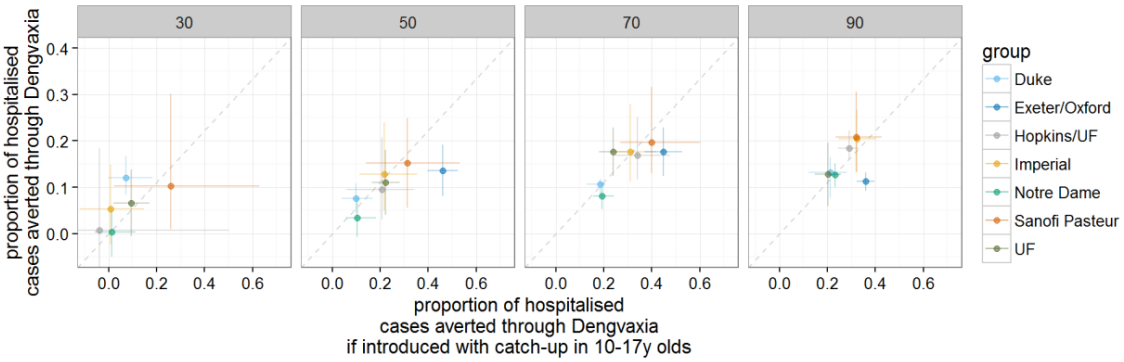

Figure 9: The proportion of hospitalised DENV cases averted in the 10 years after vaccine introduction comparing introduction according to the reference strategy to introduction by adding a 3-dose catch-up campaign among 10 to 17 year olds. The grey, dashed line represents those instances where both strategies prevent the same number of cases per dose of vaccine assuming that after 10 years the latter strategy has used 18/10 times more doses. SP9=10% scenario not shown for clarity (most models predicted an increase in long-term population risk of DENV hospitalisations for this scenario).

Impact of catch-up campaigns

Adding a one-off 3-dose catch-up campaign among 10 to 17 year olds (at 80% coverage) in the first year of introduction to the default policy of routine vaccination of 9 year-olds increased the impact of vaccination. The impact of such a one-off campaign was most visible in the first few years. The transient protection against DENV infection induced in a large proportion of school age children by

the catch-up campaign led to a small temporary reduction in transmission in some of the models. Most models predicted that a one-off catch-up campaign prevented a similar number of DENV hospitalisations per dose of vaccine delivered as the baseline routine vaccination strategy (Figure 9).

Effect of changing age for routine vaccination

Alternative ages for routine vaccination were explored in the range 9-18 years. In the highest transmission setting (SP9=90%), vaccination at age 9 gave the largest impact on symptomatic and hospitalised cases, leading to a 12-27% reduction in hospitalised cases compared to a 6% to 14% reduction if 16y olds are vaccinated. Varying the age of routine vaccination between 9y and 18y in settings with SP9=50% or 70% showed that the maximal difference in the proportion of hospitalised cases averted is smaller than 5% for most models. Although the predicted optimal age of vaccination varied, in most models this was 10-14y for SP9=70% and at the maximum age that was evaluated for SP9=50%. In low transmission settings (SP9=30%) all models predicted that the highest impact was achieved when vaccinating at the highest age examined. In settings with SP9≥30%, all models predicted a beneficial population impact on both symptomatic and hospitalised cases if vaccination is targeted at individuals 14 years of age or older.

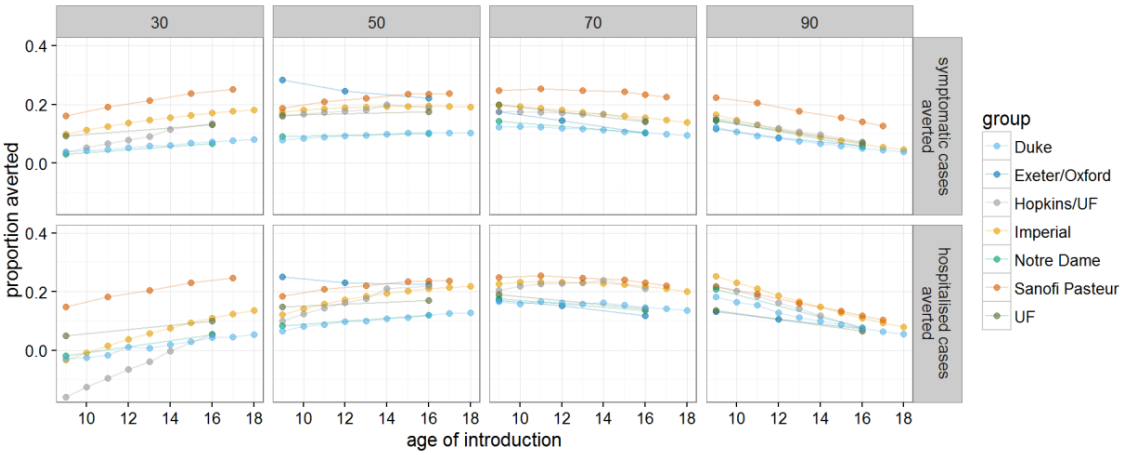

Figure 10: The proportion of symptomatic and hospitalised DENV cases averted in the 30 years after vaccine introduction. Each point represents a model realisation at a given age of vaccine introduction.

Cost-effectiveness

Using base case economic assumptions (3% discounting of costs and DALYs, threshold cost per DALY averted of $2,000, public health care provider perspective and Brazil-like costs), the threshold cost per vaccinated person in the 50-90% seroprevalence setting was predicted to be in the range $15-$40. Vaccination was most cost-effective (*i.e.* highest threshold cost per vaccinated person) for SP9=70% in all but one model.

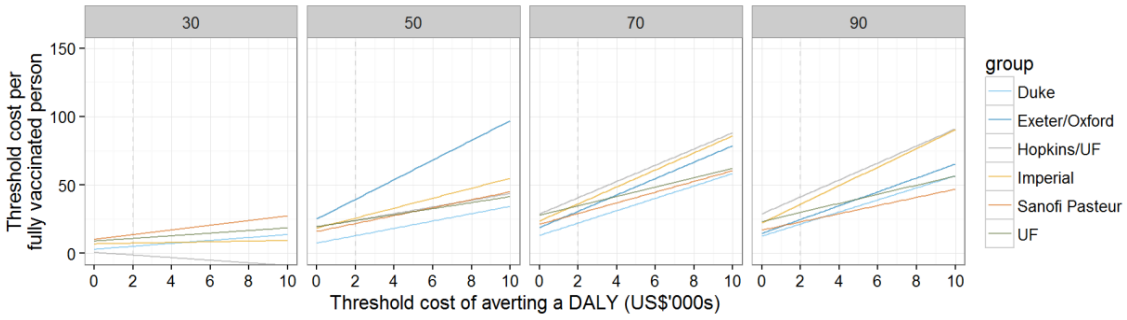

Figure 11: Threshold costs per fully vaccinated person in reference to thresholds of the cost of averting a DALY. Cost and health outcomes are calculated for 30 years after the introduction of Dengvaxia® to 9y olds with 80% coverage and without a catch-up campaign. The healthcare provider's perspective is taken and both health and costs are discounted at 3%.

We did not examine cost-effectiveness in very low transmission settings (SP9=10%) since nearly all models predicted negative health outcomes of vaccination in such contexts. In low transmission intensity settings (SP9=30%), most models predicted a threshold cost per vaccinated person in the range $5-$15. However there was one outlier: the threshold cost per vaccinated person was slightly negative in the Hopkins model, suggesting that the disbenefits of vaccination outweighed the benefits in that setting.

Results were comparable when health effects were undiscounted and the threshold cost per DALY averted is reduced to $800 (Appendix Figure 2; for comparability with past health economic analyses, see section 5). The threshold cost per vaccinated person was always $50. The same range of threshold costs per vaccinated person are seen if Philippines-like costs are used instead of Brazil-like costs (Appendix Figure 3).

However, higher threshold costs per vaccinated person are seen if the threshold cost per DALY averted under base case economic assumptions is increased to $10,000 or a societal perspective is adopted. At $10,000 per DALY averted, the threshold cost per vaccinated person rose to up to $100 for most models. Taking a societal perspective, the threshold cost per vaccinated person can exceed $150 in high transmission intensity settings (SP9=70-90%) (Appendix Figure 4).

At a threshold cost per DALY averted of $2,000, most of the benefit of vaccination in all the models comes from averting health care costs rather than DALYs. However, at a threshold cost per DALY averted of $10,000, the value of DALYs averted becomes more important than health care costs averted. The majority of DALYs averted come from preventing deaths rather than non-fatal dengue episodes (based on sensitivity analyses from a selection of models; Appendix Figure 5). Since the CFR of dengue and the impact of vaccination on dengue mortality are uncertain and not directly informed from trials, the uncertainty around estimates with a high threshold cost per DALY averted is greater than when the threshold cost per DALY averted is at $2,000.

In line with the model predictions for health impacts, cost-effectiveness is maintained (or even improved) for later ages of vaccination except in the 90% seroprevalence setting. The incremental cost-effectiveness of a one-off catch-up policy was found to be similar to that of vaccinating 9 year olds routinely in moderate transmission settings, but lower in the highest (SP9=90%) transmission intensity setting. This suggests that in moderate transmission intensity settings, the decision to implement a catch-up campaign should be driven by affordability considerations.

Furthermore, the potential impact of dengue vaccination of 9 year olds at 80% coverage on catastrophic payments and medical impoverishment for a Malaysia-like setting was evaluated (for details see Appendix (3): C*atastrophic payments and medical impoverishment*). In brief: using Malaysia specific data on income quantiles and medical expenses it was estimated that the burden of catastrophic expenses in this setting scales linearly with the burden of hospitalisation and that for every averted hospitalised case of dengue approximately 0.0357 catastrophic payments and 0.0069 medical impoverishments can be averted.

8. Conclusions

Impact in moderate to high transmission intensity settings

All models predicted that routine vaccination of 9 year olds with Dengvaxia® at 80% vaccine coverage would cause an overall reduction in dengue disease in moderate to high transmission intensity settings (SP9≥50%). For reference, this range of transmission intensity covers all the sites selected for the phase III trials of Dengvaxia®. The impact of vaccination was greatest in high transmission intensity settings (SP9≥70%), where the reduction in DENV-related hospitalisations predicted by the models ranged from 10 to 30% percent, with 20% being an approximate central value. Predicted impact on all symptomatic dengue disease were generally comparable to impact on hospitalised disease in these transmission settings.

Impact in low transmission intensity settings

Most models predicted that in very low transmission intensity settings (SP9=10%), vaccination is likely to increase dengue hospitalisation rates. This is because in such settings, a high proportion of individuals were expected never to experience a natural secondary dengue infection. Vaccination, which is assumed to prime seronegative recipients to have a 'secondary-like' infection, can therefore increase incidence of symptomatic and hospitalised dengue in such a setting.

In settings with slightly higher (but still low) transmission intensity (SP9=30%) there was less consensus between the predictions of different models; those models which better reproduced the risk increase in 2-5 year olds in the long-term follow-up tended to predict that vaccination at age 9 would increase hospitalisations in this setting while other models predicted a beneficial effect of vaccination. All models, however, indicated that routine vaccination would be of net benefit when targeted at 14 year olds or older.

Overall the predicted impact of Dengvaxia® were always modest, being <20% for nearly all models, even when ages of vaccination above 9 years were considered.

Effect of varying coverage and catch-up campaigns

All models predicted that the most of the impact of vaccination was due to direct effects, particularly in moderate to high transmission settings. As a consequence the predicted long-term impact of vaccination scaled approximately linearly with the number of people vaccinated when different coverage levels were examined and when the potential impact of a catch-up campaign was explored.

Age at vaccination

All models found that as transmission intensity increased, the optimal age for routine vaccination, in terms of vaccination impact, decreased. Within the age range considered in this exercise (9-18y) vaccination at 9 years (the lower age limit for licensed use of Dengvaxia®) was optimal for the highest transmission intensity settings (SP9=90%). Vaccination at between 11 and 13 years was near-optimal for the SP9=70% setting for most models, although within the explored age-range the

predicted impact of vaccination was relatively insensitive to the age of vaccine recipients. The optimal age range increased to 14-18 years in the SP9=50% moderate transmission setting, and all but one model predicted targeting 16-18 year olds would be preferred in the SP9-30% low transmission intensity setting. All models predicted a positive impact on dengue disease in all settings with SP9≥30% if vaccination targeted children aged 14 years or older.

Cost-effectiveness

Vaccination was predicted to be potentially cost-effective in settings with SP9=30-90%, if the vaccine can be purchased and delivered cheaply enough. However, the consensus of the modelling indicated that vaccination will only be cost-effective using base case economic assumptions if the total cost of fully vaccinating one person is below $40 ($15 at SP9=30%). Given that the recurrent costs of delivering three doses of HPV vaccine in a similar age group in low and middle income countries lies in the range $1 - $16 [36], vaccination is may not be cost-effective in the SP9=30% setting and vaccine would have to be competitively priced and/or co-administered with other vaccines to be cost-effective in higher transmission settings.

Vaccination was predicted to more cost-effective if a societal perspective is adopted or a higher cost per DALY averted is assumed, with threshold costs per vaccinated person rising to $100-$150.

All health-economic results are indicative only, and are not a substitute for single-country economic evaluations using local data to inform national procurement decisions.

Major uncertainties

All models adopted biological assumptions regarding vaccine action that the SAGE working group felt best reflected current understanding. However, current limitations of the available trial data mean uncertainties remain regarding the level of protection provided against disease versus infection and the rate at which protection declines. In particular, the assumption that vaccination acts in a similar way to natural infection in priming or boosting immunity is consistent with the phase III trial results, but cannot be directly validated given the lack of information on impact on asymptomatic infections as well as baseline serostatus in >80% of trial participants.

In addition, there is little evidence for the impact of a breakthrough infection on the immune state of a seronegative vaccinee; all models made the plausible (but optimistic) assumption that such individuals would have immunity comparable to that of someone who had experienced two natural infections [19], but there is no data available to compare this and other plausible scenarios.

While not required to fit the aggregate trial data used for model validation here, we also cannot rule out there might be intrinsic variation in vaccine efficacy with age, independent of serostatus; if efficacy is higher in older recipients, vaccine impacts are likely to be larger than presented here (or less detrimental in low seroprevalence settings). Vaccine efficacy may also vary by serotype (independent of serostatus); only the Sanofi model was able to explore this in detail, as trial data disaggregated by both country and serotype (needed to fit to serotype-specific efficacies) are not currently publically available.

Last, underlying uncertainties about dengue epidemiology also affected this modelling. Perhaps the most pertinent to the predictions of vaccine impact shown is the relationship between symptoms and infectiousness. Whereas many of the models assumed that symptomatically infected individuals were substantially more infectious than those who were asymptomatic, several others assumed that symptoms did not alter infectiousness. Empirical evidence for a relationship between symptoms and infectiousness is mixed [37,38]. If infectiousness is not correlated with disease, the impact of

vaccination in the respective models in the high transmission settings is likely to be slightly less than presented here, while the impact in low transmission settings is likely to be slightly greater.

9. Acknowledgements

We are grateful to Celina Martelli, Dagna Constenla, Don Shepard, Vittal Mogasale and Yot Teerawattananon for advice on the health economic evaluation; Sarah Cox for help deriving economic parameters; Chiu Wan Ng and Lucy Chai-See Lam for conducting the catastrophic payment and impoverishment analysis; Kirsten Vannice, Joachim Hombach and Raymond Hubertussy for their supportr and valuable advice during CMDVI; members of the SAGE-WG on dengue who provided frequent feedback on model assumptions and introduction scenarios of interest and to members of the IVIR-AC committee for their technical review of both process and results.

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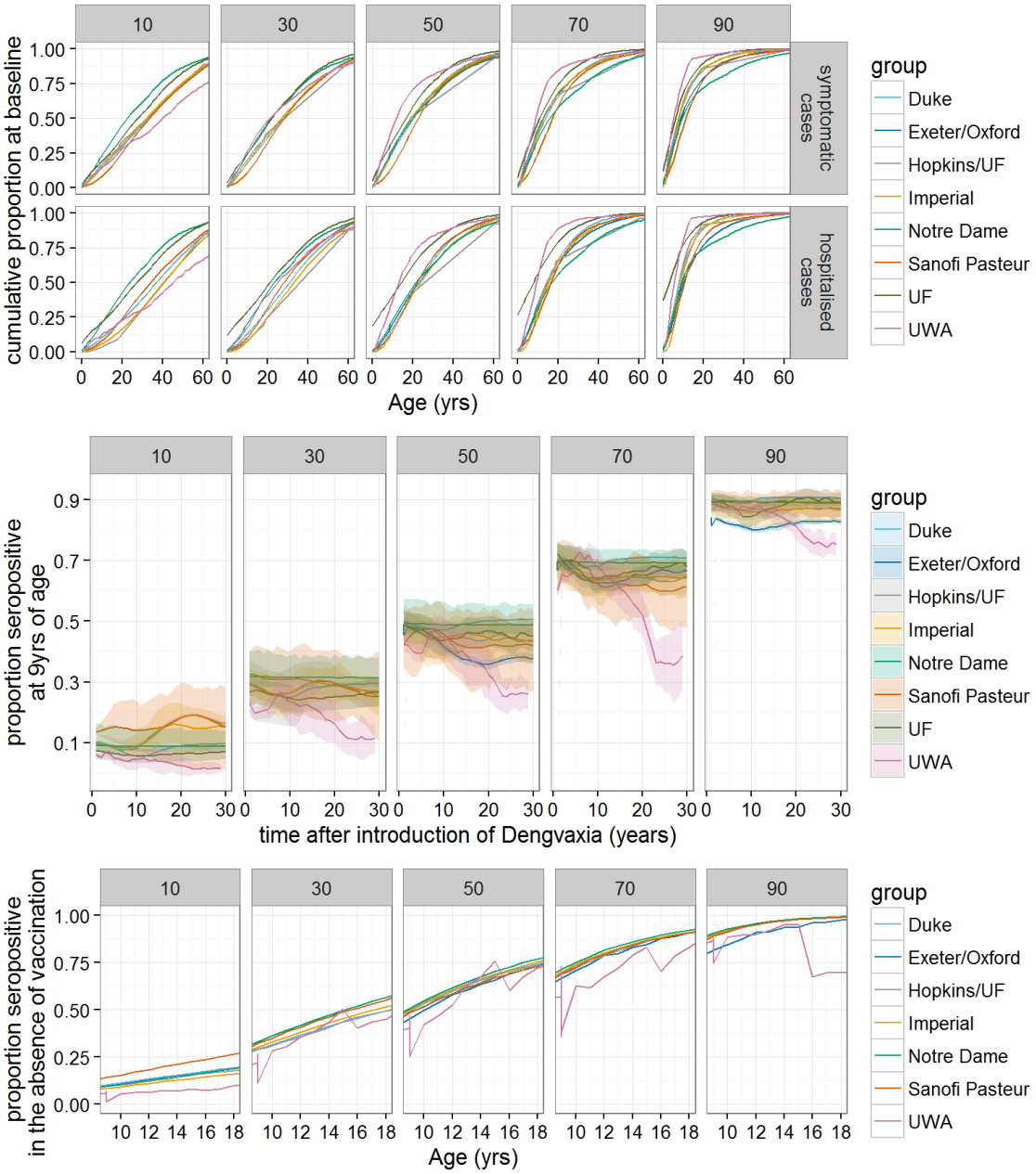
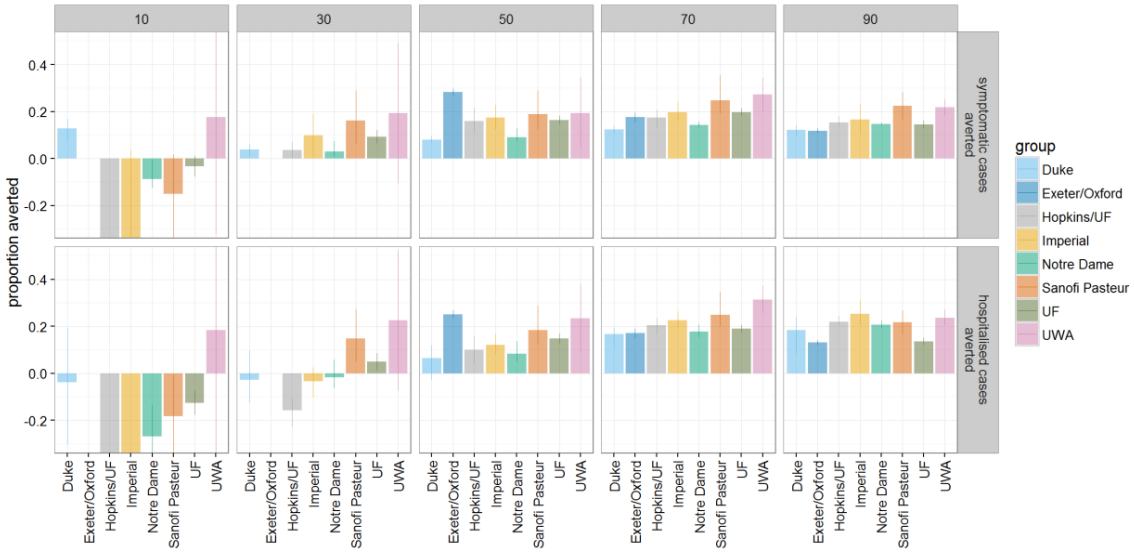
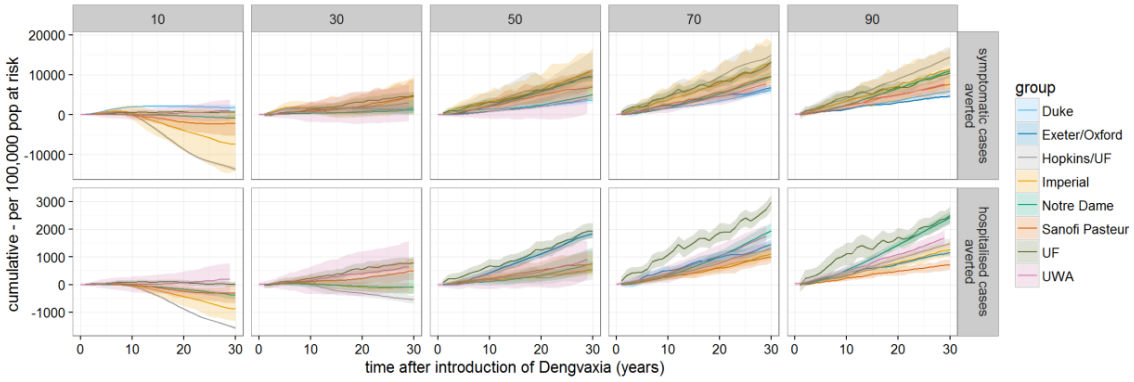
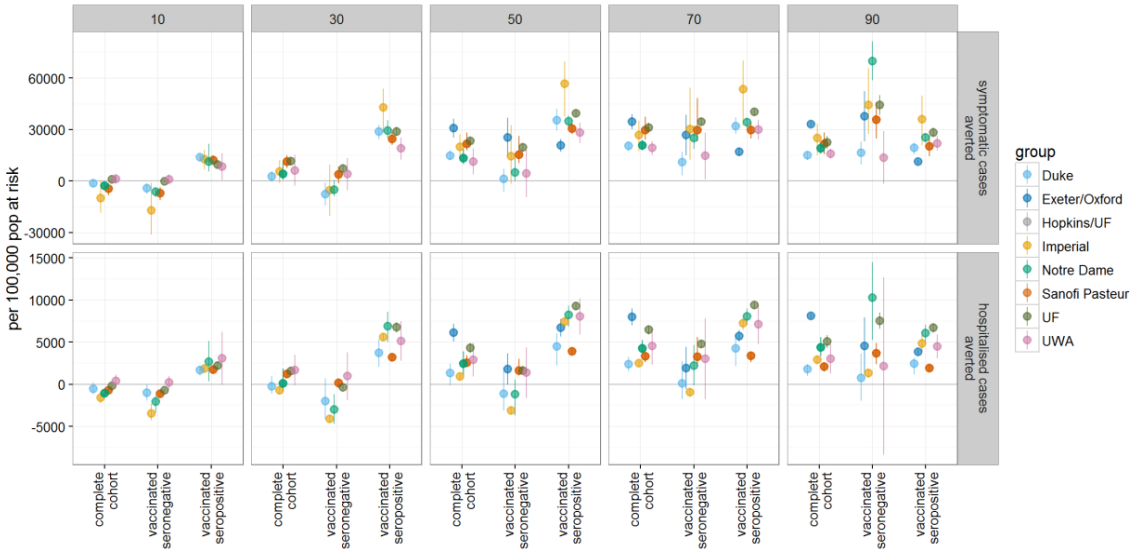
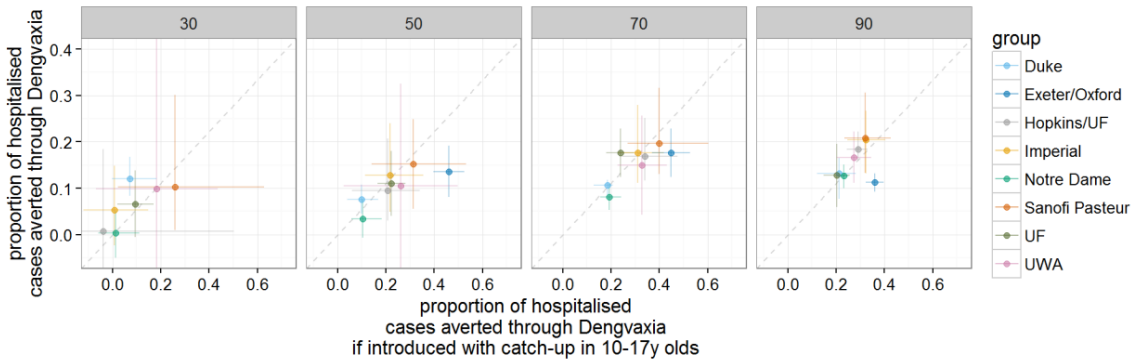
11. Appendix (1): Results including the UWA model

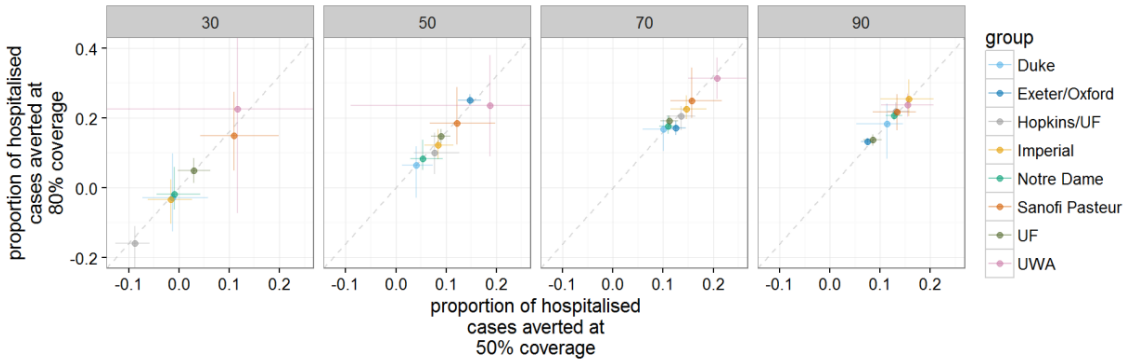


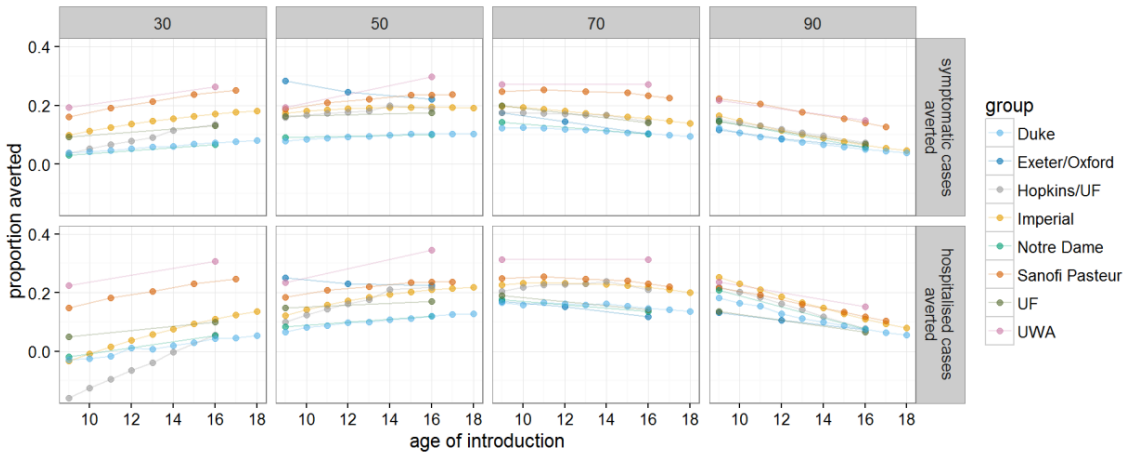

10
30
50
70
90
symptomatic cases averted
hospitalised cases averted
proportion averted
0.4
0.2
0.0
-0.2
Duke
Exeter/Oxford
Hopkins/UF
Imperial
Notre Dame
Sanofi Pasteur
UF
UWA
group

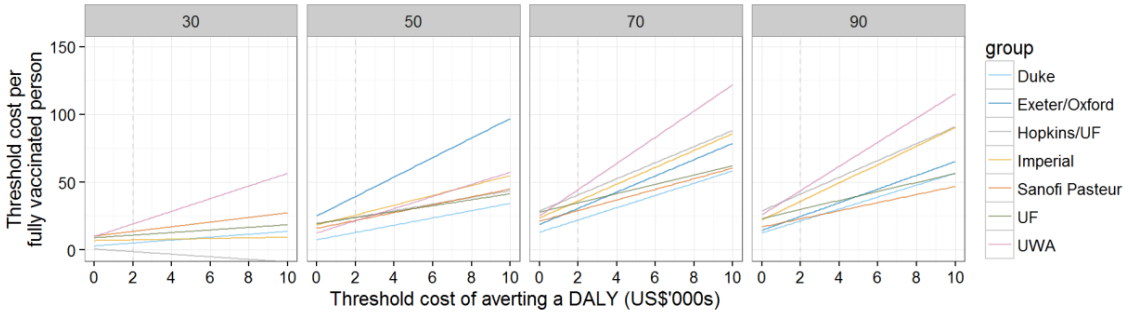

10
30
50
70
90
symptomatic cases averted
hospitalised cases averted
cumulative - per 100,000 pop at risk
20000
10000
0
-10000
3000
2000
1000
0
-1000
0
10
20
30
time after introduction of Dengvaxia (years)
group
Duke
Exeter/Oxford
Hopkins/UF
Imperial
Notre Dame
Sanofi Pasteur
UF
UWA


10
30
50
70
90
symptomatic cases averted
hospitalised cases averted
per 100,000 pop at risk
60000
30000
0
-30000
15000
10000
5000
0
-5000
complete cohort
vaccinated seronegative
vaccinated seropositive
group
Duke
Exeter/Oxford
Hopkins/UF
Imperial
Notre Dame
Sanofi Pasteur
UF
UWA

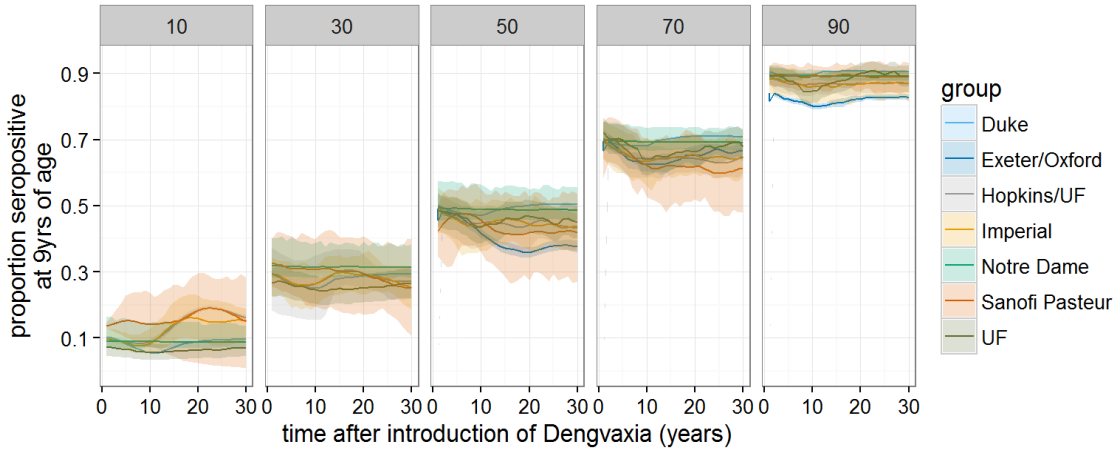

30
50
70
90
proportion of hospitalised cases averted through Dengvaxia
0.0
0.1
0.2
0.3
0.4
0.0
0.2
0.4
0.6
proportion of hospitalised cases averted through Dengvaxia if introduced with catch-up in 10-17y olds
group
Duke
Exeter/Oxford
Hopkins/UF
Imperial
Notre Dame
Sanofi Pasteur
UF
UWA


30
50
70
90
proportion of hospitalised cases averted at 80% coverage
-0.2
0.0
0.2
0.4
-0.1
0.0
0.1
0.2
proportion of hospitalised cases averted at 50% coverage
group
Duke
Exeter/Oxford
Hopkins/UF
Imperial
Notre Dame
Sanofi Pasteur
UF
UWA

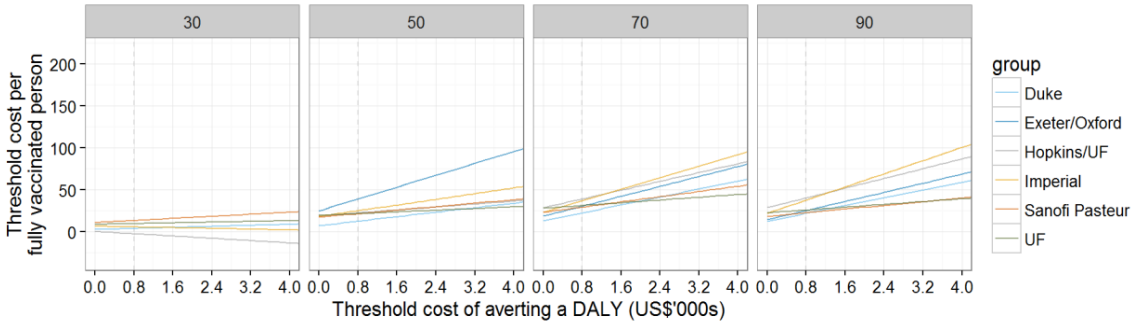

30
50
70
90
symptomatic cases averted
hospitalised cases averted
proportion averted
0.0
0.2
0.4
10
12
14
16
18
age of introduction
group
Duke
Exeter/Oxford
Hopkins/UF
Imperial
Notre Dame
Sanofi Pasteur
UF
UWA


30
50
70
90
Threshold cost per fully vaccinated person
0
50
100
150
0
2
4
6
8
10
Threshold cost of averting a DALY (US$'000s)
group
Duke
Exeter/Oxford
Hopkins/UF
Imperial
Sanofi Pasteur
UF
UWA

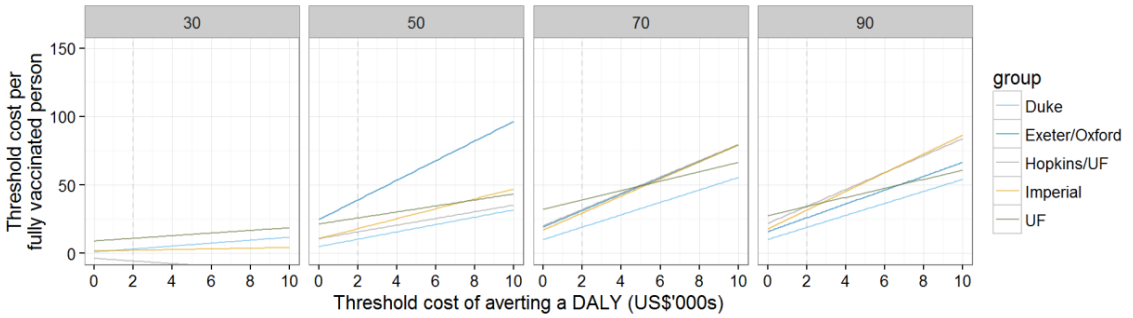
12. Appendix (2): Further supporting material



Appendix Figure 1: The change in proportion of 9y old children that are seropositve at vaccination in the 30 years after the introduction of Dengvaxia®. Lines represent the mean and the shaded region of the respective colour the 95% range over multiple simulations

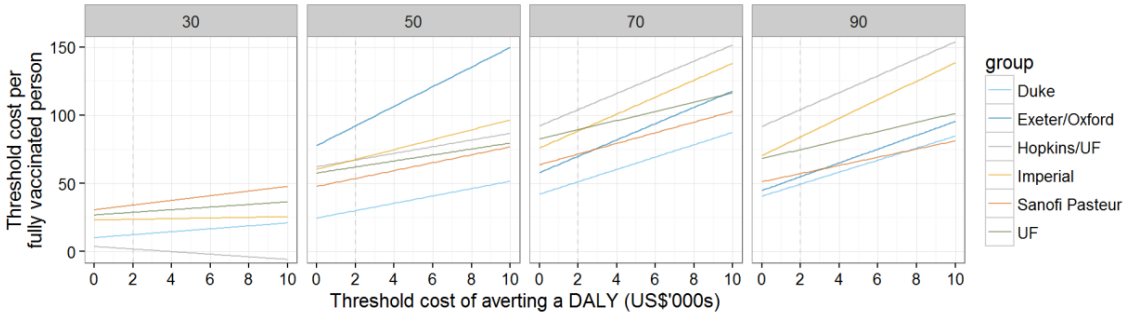


Appendix Figure 2: Threshold costs per fully vaccinated person in reference to thresholds of the cost of averting a DALY. Cost and health outcomes are calculated for 30 years after the introduction of Dengvaxia® to 9y olds with 80% coverage and without a catch-up campaign. The healthcare provider's perspective is taken and only costs are discounted at 3%.

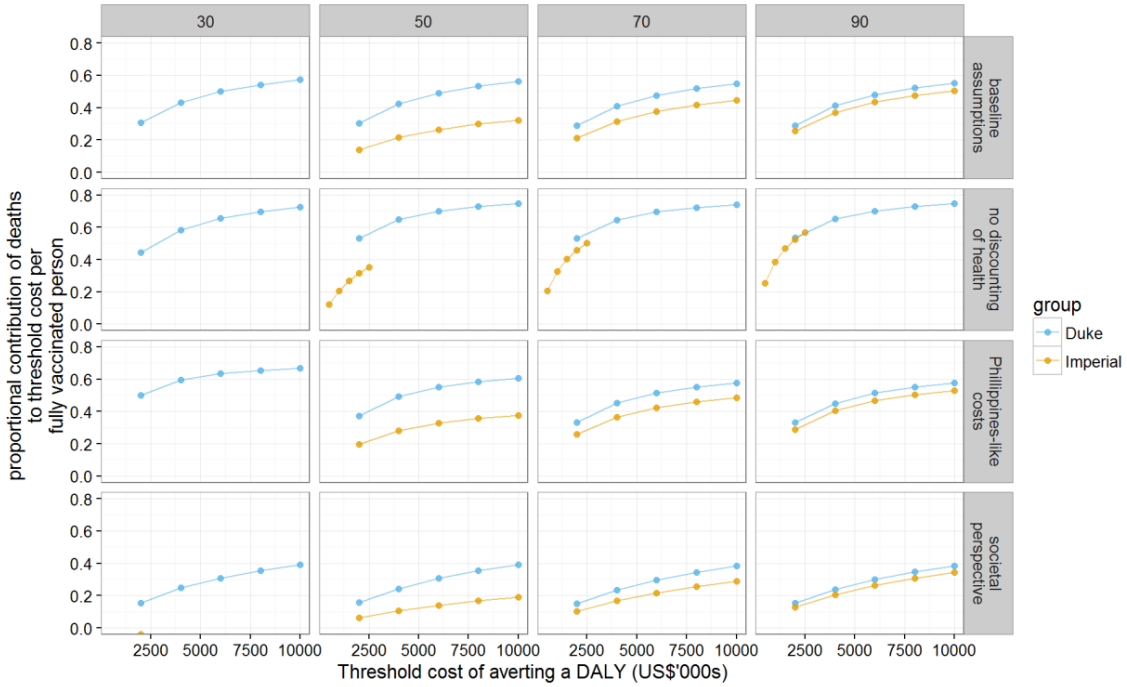


Appendix Figure 3: Threshold costs per fully vaccinated person in reference to thresholds of the cost of averting a DALY. Cost and health outcomes are calculated for 30 years after the

introduction of Dengvaxia® to 9y olds with 80% coverage and without a catch-up campaign. The healthcare provider's perspective is taken and both health and costs are discounted at 3%. Costing values are assumed to reflect a lower-middle income Asian country



Appendix Figure 4: Threshold costs per fully vaccinated person in reference to thresholds of the cost of averting a DALY. Cost and health outcomes are calculated for 30 years after the introduction of Dengvaxia® to 9y olds with 80% coverage and without a catch-up campaign. The societal perspective is taken and both health and costs are discounted at 3%.



Appendix Figure 5: The proportion of the threshold costs per fully vaccinated person that is due to deaths averted; for vaccination of 9 year olds at 80% coverage assessed over 30 years after the start of routine vaccination.

Appendix Table 1: Parameter assumptions on progression probabilities from asymptomatic infection through to death, on the variance in transmissibility with severity, and on variation from the baseline vaccine mode of action. Ranges indicate the 95% range of the posterior estimates.

MODEL General info		Sanofi Pasteur	Hopkins / UF	Imperial	Duke	UF	UWA	Notre Dame	Exeter / Oxford
Factor by which transmissibility is increased in symptomatic infections		4	2	2	1	2x / 3x for mild / severe infections	1	1.1-1.23	1
Proportion of VCD among infections	primary infection	from 10% (<5 y) to 31% (>15 yrs)	53%	45% (30%-70%)	34.2% (27.1% - 41.4%)	45%	30%	30%	32%
	secondary infection	from 16% (<5 y) to 52% (> 15 yrs)	100%	85% (55%-100%)	71.4% (64.4% - 78.6%)	60%	60%	60%	38%
	tertiary infection	from 4% (<5 y) to 13% (> 15 yrs)	23%	11% (6%-17%)	13.6% (9.8% - 17.8%)	10%	10%	10%	12%
	quarternary infection	from 4% (<5 y) to 13% (> 15 yrs)	0%	same as tertiary	Assumed same as tertiary	10%	10%	10%	12%
	age dependency?	yes	no	no	no	no	no	no	yes
Proportion of hospitalised cases among VCD	primary infection	~4% of infections (~11% of cases)	0%	0.5% of infections (~1% of cases)	5.3% of cases (0.2% - 15.1%)	all severe cases, ~10% mild cases	11.1%	11.1%	3%
	secondary infection	~7% of infections (~15% of cases)	14%	10% of infections (~12% of cases)	11.2% of cases (7.2% - 15.4%)	ibid	20.9%	20.9%	11%
	tertiary infection	~1% of infections (~7% of cases)	0%	0.1% of infections (~0.9% of cases)	4.0% of cases (0.02% - 14.4%)	ibid	5.2%	5.2%	2%
	quarternary infection	~1% of infections (~7% of cases)	0%	0.1% of infections (~0.9% of cases)	Assumed same as tertiary	ibid	5.2%	5.2%	2%
	age dependency?	yes	no	no	no	no	no	no	yes
proportion of deaths among VCD		~0.05% (0.5% of hospitalised)	~ 0.03% (0.4% of hospitalised)	~0.05% (0.5% of severe cases)	0.078%	0.078% of hospitalised	0.078%	0.078%	~0.084% (0.4% of hospitalised)
Differences to the baseline vaccine mode of action assumption		serotype specific efficacy; increasing with severity and, in seronegative vaccinees, with doses	none	none	none	none	life-long protection against infection of seropositive vaccinees	life-long protection against infection of seropositive vaccinees	serotype specific protection against infection; life-long in seropositive vaccinees

Appendix Table 2: Overview of costs and ICER of alternative intervention strategies to prevent dengue and of alternative vaccines.

INTERVENTION	COUNTRY	COST PER UNIT	ICER	CURRENCY	REFERENCE	PERSPECTIVE
Hpv vaccination of 12-year olds	Brazil	13.5	1,290	2011 USD	[27]	HCP
Hpv vaccination of 12-year olds	Philippines	13.5	1,590	2011 USD	[27]	HCP
Hpv vaccination of 12-year olds	PAHO upper middle income countries min	13.5	630	2011 USD	[27]	HCP
Hpv vaccination of 12-year olds	PAHO upper middle income countries max	13.5	2,080	2011 USD	[27]	HCP
Hpv vaccination of 12-year olds	WPRO lower middle income countries min	13.5	260	2011 USD	[27]	HCP
Hpv vaccination of 12-year olds	WPRO lower middle income countries max	13.5	15,000	2011 USD	[27]	HCP
Infant pcv7 vaccination	Latin America & the Caribbean	10	1,168	2005 USD	[28]	HCP
Infant pcv7 vaccination	Latin America & the Caribbean	10	685	2005 USD	[28]	Societal
Infant rotavirus vaccination	Americas upper middle income countries	7.5	506	2007 USD	[29]	HCP
Infant rotavirus vaccination	Western Pacific lower middle income countries	7.5	439	2007 USD	[29]	HCP
Case management of dengue	Developed health system	200	587	1993 USD	[30]	HCP
Vector chemically controlled (vs case management alone)	Developed health system	0.46	6,568	1993 USD	[30]	HCP
Environmental vector control (vs case management alone)	Developed health system	2.25	13,696	1993 USD	[30]	HCP
Vector chemically controlled (vs do nothing)	Undeveloped health system	0.46	1,992	1993 USD	[30]	HCP
Environmental vector control (vs do nothing)	Undeveloped health system	2.25	3,668	1993 USD	[30]	HCP
Gdp per capita	Brazil	-	11,000	2013 USD	World Bank	-
Gdp per capita	Philippines	-	2,765	2013 USD	World Bank	-

13. Appendix (3): *Catastrophic payments and medical impoverishment*

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An independent analysis of the impact of dengue vaccines on catastrophic health payments and medical impoverishment due to dengue in Malaysia was conducted independently, using output from the eight models. The dengue burden in Malaysia has been increasing in recent years. In 2014 there were 361 dengue cases per 100 000 population (Ministry of Health Malaysia, 2015), more than double the incidence rate of 152 per 100 000 population in 2010 (Ministry of Health Malaysia, 2010). Health care provision in Malaysia is split between public and private healthcare providers. The public health system is financed through general taxation and user fees have been kept low to

ensure affordability. Dengue patients are entitled to free public treatment but private health care is paid for mainly through out-of-pocket (OOP) payments and fees charged are much higher than those in the public sector.

Appendix Table 3: Population at risk, Malaysia 2003

Age groups	Household Income Quintiles[1]					
	Poorest	2nd	Middle	3rd	Richest	Overall
<9 years	1,234,500	1,629,900	974,300	1,406,000	1,079,400	6,324,100
9-18 years	1,032,900	1,434,700	758,000	1,030,800	811,700	5,068,100
19+ years	2,260,100	3,525,700	2,178,100	3,580,000	2,720,800	14,264,700
overall	4,527,500	6,590,300	3,910,400	6,016,800	4,611,900	25,656,900

Note:
Breakdown of 2003 population into income quintiles by average gross household income of states and territories in Malaysia

This study used data from various sources. The patient level OOP payments for an episode of dengue illness were derived from two datasets of dengue patients collected in 2003. The first dataset contained information of 552 dengue patients who had been admitted to four hospitals (two public and two private hospitals) in Selangor, a state in Malaysia. The second contained information of 137 dengue patients in Selangor who received purely ambulatory care services, either from private or public health providers or both. In addition to patients' OOP payments for dengue treatment, these datasets also contained information of patients' household income. This allowed for an estimation of catastrophic health payments and medical impoverishment by household income quintiles. These estimates were then applied to the 2003 national population (Appendix Table 3). Levels of catastrophic health payments and medical impoverishment averted by dengue vaccination were estimated using modelling results from CMDVI.

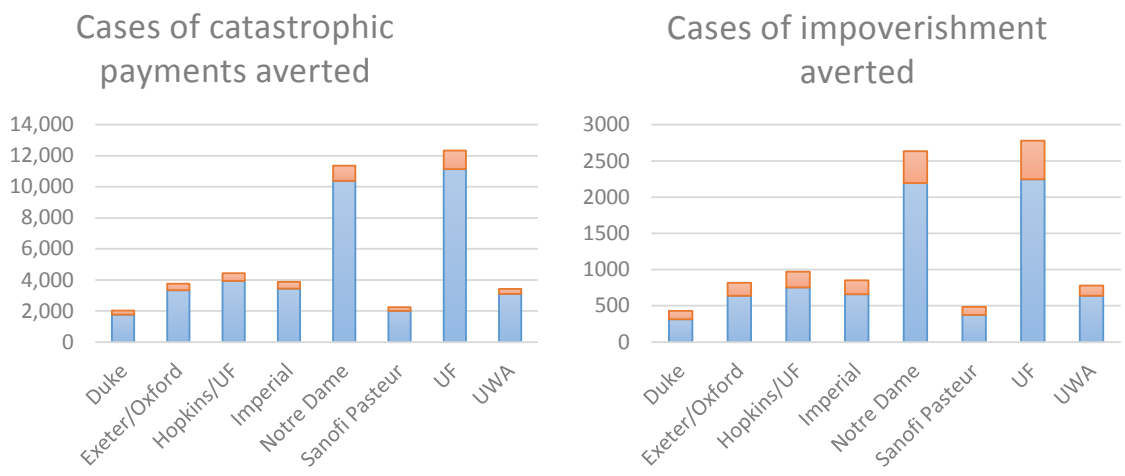
Appendix Table 4: Incidence of catastrophic payments and impoverishment across income quintiles due to dengue in Malaysia

	Household Income Quintiles					
	Poorest	2nd	Middle	3rd	Richest	Overall
Proportion private hospital admissions	4.78%	9.26%	7.31%	22.40%	43.61%	16.09%
Incidence of catastrophic payments[1]						
Private hospital admissions	40.00%	36.36%	37.50%	17.39%	8.77%	18.75%
Public hospital admissions	0.81%	0.00%	0.00%	1.18%	0.00%	0.45%
Incidence of medical impoverishment[2]						
Private hospital admissions	40.00%	9.09%	0.00%	0.00%	0.00%	2.68%
Public hospital admissions	0.81%	0.00%	0.00%	0.00%	0.00%	0.23%

Note:
[1]Catastrophic payment defined as out-of-pocket direct medical costs related to dengue admission exceeding 10% of annual household income.
[2]Medical impoverishment defined as annual household income falling below annualised monthly household poverty line after netting out OOP direct medical costs related to dengue admission.

The analysis showed that catastrophic health payments and medical impoverishment only occurred among hospitalised dengue patients and none among patients who received purely ambulatory care

(Appendix Table 4). As a result, cases of impoverishment and catastrophic payments were approximately a multiplier of hospitalisation incidence in the modelled Malaysian setting. As expected there were higher levels among patients who had been hospitalised in private hospitals and much lower levels among patients hospitalised in public hospitals. The effect of vaccination on levels of catastrophic health payments and medical impoverishment for dengue care at various dengue model transmission settings differed between modelling groups. In general, the greatest reduction were found in higher transmission settings while at lower transmission settings, some models predicted increased levels of catastrophic payments and medical impoverishment. At the highest transmission setting (SP9=90), vaccination is predicted to avert 8.7% to 23.7% of catastrophic payment cases and 8.3% to 25.8% of medical impoverishment cases over 10 years (Appendix Figure 6).



Appendix Figure 6: The predicted number of cases of impoverishment and catastrophic payment averted within 10 years after the start of vaccination in a SP9=90% setting. Blue bars indicate private admissions and red bars public admission.